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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan Title	**RESOLUTE ONYX China RCT Study** A Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in Comparison with the Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System in the Treatment of Subjects Eligible for Percutaneous Transluminal Coronary Angioplasty (PTCA) in China
Study Device Name	Study Arm: Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Control Arm: Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System
Model/Specification	Refer to Table 7-1 and Table 7-2
Classification of Study Device	Class III
Class III Medical Device Fulfil Clinical Trial Approval	No
Similar Device Marketed in China	Yes
Document Version No. and Date	2.0, 13-Feb-2019
Lead Site	Fuwai Hospital, Chinese Academy of Medical Sciences No.167 North Lishi Road, Xicheng District, Beijing, China
Coordinating Investigator	Dr. Yongjian Wu
Sponsor	Medtronic, Inc. 710 Medtronic Parkway, Minneapolis, MN 55432, USA
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1. Investigator Statement

1.1. Read and Approved by Investigator

Clinical Investigation Plan Title:	**RESOLUTE ONYX China RCT Study** A Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in Comparison with the Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System in the Treatment of Subjects Eligible for Percutaneous Transluminal Coronary Angioplasty (PTCA) in China
Sponsor:	Medtronic, Inc.
Local Sponsor/Agent:	Medtronic (Shanghai) Management Co., Ltd
Version Number/Date:	2.0, 13-Feb-2019

I hereby confirm below:

- I will conduct this study in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the Clinical Investigation Plan (CIP).
- I will ensure accuracy, completeness and timeliness of the data reported in the Case Report Forms and in all other study required reports, and complete the final study report on time.
- The study devices will be used only for this study and the receipt and use of the study devices will be recorded completely and accurately and the records will be retained during the process of the clinical study.
- The Medtronic authorized monitor, auditor and the regulatory authorities have the right to conduct monitoring, audit and inspection for this study.
- The clinical study should be conducted in strict compliance with the clinical study agreement signed by all parties.

I have read this version of the Clinical Investigation Plan of RESOLUTE ONYX China RCT Study, including all appendices and the above statements. I fully agree all the above requirements and will ensure that the study is conducted as described herein.

Investigator Comment: _____
Investigator's Name (Print): _____
Institution: _____
Investigator's Signature: _____
Date (dd/mmm/yyyy): _____

1.2. Read and Approved by Clinical Research Institution

Clinical Investigation Plan Title:	**RESOLUTE ONYX China RCT Study** A Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in Comparison with the Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System in the Treatment of Subjects Eligible for Percutaneous Transluminal Coronary Angioplasty (PTCA) in China
Sponsor:	Medtronic, Inc.
Local Sponsor/Agent:	Medtronic (Shanghai) Management Co., Ltd
Version Number/Date:	2.0, 13-Feb-2019
Institution Name/Site Name	_____
Comments of Clinical Research Institution	_____
Signature / Stamp	_____
Date (dd/mmm/yyyy):	_____

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2. Glossary

Acronym/Abbreviation	Term
% DS	Percent diameter stenosis
ACC	American College of Cardiology
AE	Adverse event
AHA	American Heart Association
CABG	Coronary artery bypass graft
CASS	Coronary Artery Surgery Study
CCSC	Canadian Cardiovascular Society Classification
CE	Conformité Européenne
CEC	Clinical Events Committee
CFDA	China Food and Drug Administration
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTO	Chronic Total Occlusion
DES	Drug eluting stent
DS	Diameter stenosis
DAPT	Dual Anti-Platelet Therapy
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EU	European Union
GCP	Good Clinical Practices
GI	Gastrointestinal
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IFU	Instructions for Use
FAS	Full Analysis Set
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LIMA	Left internal mammary artery
ISO	International Organization for Standardization

LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
mg	Milligram
MI	Myocardial infarction
MLD	Minimum luminal/lumen diameter
µg	Microgram
mm	Millimeter
NHLBI	National Heart, Lung, and Blood Institute
PCI	Percutaneous coronary intervention
PP set	Per protocol set
PTCA	Percutaneous transluminal coronary angioplasty
QCA	Quantitative coronary angiography
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
SAP	Statistical Analysis Plan
SCAI	Society for Cardiovascular Angiography and Interventions
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
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
US	United States
WHO	World Health Organization

3. Synopsis

Study Title: RESOLUTE ONYX China RCT Study A Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in Comparison with the Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System in the Treatment of Subjects Eligible for Percutaneous Transluminal Coronary Angioplasty (PTCA) in China	
Purpose	This pre-market study is initiated for Resolute Onyx CFDA product registration. The purpose of this study is to evaluate the clinical safety and efficacy of the Resolute Onyx Stent System, compared to the Resolute Integrity Stent System in subjects who are eligible for percutaneous transluminal coronary angioplasty (PTCA) in *de novo* lesions amenable to treatment with either of the two stent systems in China
Study Design	Pre-Market, Prospective, Multi-center, Open-label, Randomized Controlled Trial
Study Device	Study Arm: Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Control Arm: Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System
Objective	To evaluate the safety and efficacy of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System as compared to the Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System in subjects requiring stent implantation
Primary Endpoint	In-stent Late Lumen Loss (LLL) at 9 months post procedure as measured by QCA
Secondary Endpoints	**Secondary Clinical Endpoints:** • Acute Success (device, lesion, procedure) • The following secondary endpoints will be assessed at 30 days, 6 months, 9 months and annually thereafter through 5 years: - Major Adverse Cardiac Events (MACE) - Death (Cardiac and Non-cardiac) - Myocardial infarction (all MI and Target Vessel Myocardial Infarction (TVMI)) - All revascularizations (Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR) and Non-TVR) - Target Vessel Failure (TVF) - Target Lesion Failure (TLF) - Stent Thrombosis (ST) **Secondary Angiographic Endpoints (at 9 months post procedure):**

<table>
<tr><td></td><td>

In-stent and in-segment percent diameter stenosis (%DS)
In-stent and in-segment binary angiographic restenosis (BAR) rate
In-stent and in-segment minimal luminal diameter (MLD)
In-segment Late Luminal Loss

</td></tr>
<tr><td>Number of Sites</td><td>Approximately 20 study sites in China</td></tr>
<tr><td>Sample Size</td><td>Approximately 550 subjects</td></tr>
<tr><td>Randomization</td><td>1:1 randomization</td></tr>
<tr><td>Study Sites and Investigators</td><td>Refer to Appendix 9-Investigator and Institutions List</td></tr>
<tr><td>Inclusion / Exclusion Criteria</td><td>Only key criteria will be listed in the synopsis, see all criteria in section 8.3 and 8.4
<u>Key Inclusion Criteria:</u>

The subject is an acceptable candidate for treatment with a drug-eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions, and the Investigator Brochure (IB) of Resolute Onyx, and, the Instructions for Use (IFU) of Resolute Integrity
Intention to follow randomization for implanting at least one Resolute Onyx stent or one Resolute Integrity stent
The subject requires treatment of up to 3 target lesions in up to 2 separate target vessels [2 target lesions in 1 vessel (including its side branches) and 1 target lesion in a separate vessel (including its side branches)] amenable to treatment with stents with diameter from 2.25 mm to 4.0 mm
Target lesion must be de novo lesion located in a native coronary artery, with the visually estimated target reference vessel diameter (RVD) and lesion length eligible for treatment by the stent size ranges shown in below stent Size Matrix

Table 3-1 Study Arm (Resolute Onyx™ Stent Size Matrix)
<table>
<tr><td>Diameter (mm)</td><td colspan="7">Length (mm)</td></tr>
<tr><td></td><td>8</td><td>12</td><td>15</td><td>18</td><td>22</td><td>26</td><td>30</td></tr>
<tr><td>2.25</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>2.5</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>2.75</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>3.0</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>3.5</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>4.0</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>

Table 3-2 Control Arm (Resolute Integrity™ Stent Size Matrix)

<table>
<tr><td rowspan="2">Diameter (mm)</td><td colspan="9">Length (mm)</td></tr>
<tr><td>8</td><td>9</td><td>12</td><td>14</td><td>15</td><td>18</td><td>22</td><td>26</td><td>30</td></tr>
<tr><td>2.25</td><td>●</td><td>-</td><td>●</td><td>●</td><td>-</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>2.5</td><td>●</td><td>-</td><td>●</td><td>●</td><td>-</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>2.75</td><td>●</td><td>-</td><td>●</td><td>●</td><td>-</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>3.0</td><td>-</td><td>●</td><td>●</td><td>-</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>3.5</td><td>-</td><td>●</td><td>●</td><td>-</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>4.0</td><td>-</td><td>●</td><td>●</td><td>-</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
</table>

Key Exclusion Criteria:

- Serum creatinine level > 2.5 mg/dl within 7 days prior to index procedure
- Evidence of an acute STEMI within 24 hours prior to index procedure
- Any previous treatment of the target lesion, including but not limited to previous PTCA, or an in-stent restenosis (ISR) lesion
- Target lesion is in a bypass graft, including but not limited to saphenous vein graft (SVG) or a left/right internal mammary artery (LIMA/RIMA)
- Unprotected left main coronary artery disease
- TIMI flow is 0 (including but not limited to CTO lesion)
- Planned two stent treatment for bifurcated lesions (bifurcated lesions treated with provisional stenting is allowed)

</td></tr>
<tr><td>**Study Assessments**</td><td>Screening and implant procedure, heath status assessments at 30 days, 6 months, 9 months, and annual assessments from 1-5 years</td></tr>
<tr><td>**Study Duration**</td><td>The study will be conducted to allow data collection and analysis through the 5-year follow-up assessment or until the study has been formally terminated
The enrollment period is estimated to be approximately 11 months. Subjects will remain in the study with baseline, procedure, 1 month, 6 months, 9 months and annual follow-up assessments until the final study assessment (i.e. 5 Year Assessment), study exit, or death, whichever comes first</td></tr>
<tr><td>**Statistical Methods**</td><td>The primary endpoint of in-stent late lumen loss (LLL) at 9 months post procedure of the study arm will be compared to LLL of the control arm with a non-inferiority margin of 0.16 mm. A total of 550 subjects yields 98% power, assuming a two-sided type I error at 0.05 level of significance and 25% loss to follow-up rate</td></tr>
</table>

4. Introduction

4.1. Background

Coronary artery stents have shown to improve the safety and the efficacy of percutaneous coronary interventions (PCI) over balloon angioplasty alone [1, 2, 3, 4]. Notwithstanding, restenosis is still encountered in 20-40% of coronary lesions after implantation of a bare metal stent[5] , incurring frequent repeat revascularization procedures. This negatively impacts patients "quality of life and society" health care expenditures. The introduction of drug-eluting stents (DES), with localized and controlled release of anti-restenotic agents, have successfully addressed the problem of stent restenosis by demonstrating significantly less restenosis and need for repeat revascularization[6].

The Resolute Onyx Zotarolimus-Eluting Coronary Stent System (Resolute Onyx) represents Medtronic's new generation of DES which incorporates thinner stent struts and increases radiopacity over predicate stents, while retaining the essential characteristics of the Resolute Zotarolimus-Eluting Coronary Stent System (Resolute) and Resolute Integrity Zotarolimus-Eluting Coronary Stent System (Resolute Integrity). The thinner stent struts improve acute deliverability performance by way of crossing profile and flexibility. The increased radiopacity improves the acute performance by ensuring accurate and complete lesion coverage. The iterative design improvements of contemporary stents have empowered physicians with a greater ability to deliver and deploy stents in more challenging locations safely.

The RESOLUTE clinical data provide assurance to the safe and effective use of the zotarolimus drug and BioLinx polymer in over 1 million coronary stenting procedures. The Global RESOLUTE Clinical Trial Program has enrolled over 7,500 subjects in whom there is high quality, long-term outcomes data. No Resolute Onyx clinical study data are available on Chinese population so far. The RESOLUTE ONYX China RCT Study is intended to demonstrate that the efficacy observed in the Global RESOLUTE Clinical Trial Program is maintained with the iterative modifications made to the Resolute Onyx stent.

Data collected from the RESOLUTE ONYX Clinical program studies will augment the existing data generated to date in the RESOLUTE Clinical Trial Program.

The RESOLUTE ONYX Clinical Program currently includes the RESOLUTE ONYX Core

---

[1] Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. Mar 19 1987;316(12):701-706.

[2] Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, et al. for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331(8):489-495

[3] Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331(8):496-501.

[4] Kimura T, Yokoi H, Nakagawa Y, Tamura T, Kaburagi S, Sawada Y, Sato Y, Hamasaki N, Nosaka H, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med. 1996;334(9):561-566.

5 Kastrati A, Mehilli J, Dirschinger J, Pache J, Ulm K, Schuhlen H, Seyfarth M, Schmitt C, Blasini R, Neumann FJ, Schomig A. Restenosis after coronary placement of various stent types. Am J Cardiol. 2001; 87(1):34-39.

6 Lemos PA, Serruys PW, Sousa JE. Drug-eluting stents: cost versus clinical benefit. Circulation. Jun 24 2003; 107(24):3003-3007.

(2.25 mm – 4.0 mm) Clinical Study, conducted in the United States (US) and the RESOLUTE ONYX 2.0 mm Clinical Study conducted in the US and Japan, in addition to the RESOLUTE ONYX China Single Arm and RCT studies:

- The RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study successfully met both the primary endpoint and pre-specified powered secondary endpoints. The primary endpoint of in-stent late lumen loss at 8 months was compared to historical control of the RESOLUTE US Angio/IVUS Sub-Study with propensity score adjustment. The propensity score adjusted one-sided 95% confidence interval is -0.02 mm, which is less than the pre-specified non-inferiority margin (0.20 mm) therefore non-inferiority has been demonstrated ($p< 0.001$). After non-inferiority is demonstrated, pre-specified superiority is further evaluated, since the propensity score adjusted one-sided 95% CI is less than 0 mm, superiority is also met ($p = 0.029$).
- The RESOLUTE ONYX 2.0 mm Clinical Study completed subject enrollment on February 23, 2016 and currently is in the process of conducting the requisite subject follow-up assessments.

For Resolute Onyx, the zotarolimus drug and drug concentration of 1.6 $\mu g/mm^2$ of stent surface area remain the same as the predicate Resolute products. The Biolinx™ polymer and drug coating formulation also remain the same. Therefore, Resolute Onyx is expected to have the same long-term safety and effectiveness as predicate Resolute stents, with improved acute performance.

The Resolute Onyx stent received CE (Conformité Européenne) certificate initially in September 2014 and has been commercialized in 89 countries/regions worldwide. To date, international commercial experience with Resolute Onyx has demonstrated a low complaint rate quantitatively and qualitatively comparable the predicate Resolute Integrity product. The core sizes of Resolute Integrity stent have been approved for commercial use by China Food and Drug Administration (CFDA) in Feb 2016.

4.2. Purpose

This study is initiated for Resolute Onyx product registration with CFDA. The purpose of this study is to conduct a prospective, multi-center, open-label, randomized controlled evaluation of the clinical safety and efficacy of the Resolute Onyx Stent System, compared to the Resolute Integrity Stent System in subjects who are eligible for percutaneous transluminal coronary angioplasty (PTCA) in *de novo* lesions amenable to treatment with either of the two stent systems in China.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective

To evaluate the safety and efficacy of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System as compared to the Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System in subjects requiring stent implantation.

5.2. Endpoints

5.2.1. Primary Endpoint

In-stent Late Lumen Loss (LLL) at 9 months post procedure as measured by Quantitative Coronary Angiography (QCA).

5.2.2. Secondary Endpoints

Secondary Clinical Endpoints:

- Acute Success (device, lesion, procedure)
- The following secondary clinical endpoints will be assessed at 30 days, 6 months, 9 months and annually thereafter through 5 years:
  - Major Adverse Cardiac Events (MACE), defined as the composite of death, myocardial infarction (Q-wave and non-Q-wave), or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods
  - Death (Cardiac and Non-cardiac)
  - Myocardial infarction (all MI and Target Vessel Myocardial Infarction (TVMI))
  - All revascularizations (Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR) and Non-TVR)
  - Target Vessel Failure (TVF), defined as composite of cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization (TVR)
  - Target Lesion Failure (TLF) defined as the composite of cardiac death, target vessel myocardial infarction or clinically-driven target lesion revascularization (TLR)
  - Stent Thrombosis (ST) (as determined by ARC definitions)

Secondary Angiographic Endpoints (at 9 months post procedure):

- In-stent and in-segment percent diameter stenosis (%DS)
- In-stent and in-segment binary angiographic restenosis (BAR) rate (defined as ＞50% diameter stenosis (DS))
- In-stent and in-segment minimal luminal diameter (MLD)
- In-segment late luminal loss (LLL)

6. Study Design

The Medtronic RESOLUTE ONYX China RCT Study is a pre-market, prospective, multi-center, open-label, randomized controlled study aiming to enroll approximately 550 subjects from approximately 20 study sites in China who are eligible for percutaneous treatment with both Resolute Onyx stent and Resolute Integrity stent.

All subjects presenting to the cardiac catheterization laboratory for possible interventional treatment are potential candidates. Those subjects who sign the Ethics Committee (EC) approved informed consent and subsequently fulfill all inclusion criteria and no exclusion criteria will be enrolled in the trial and will be randomized using an interactive web response system (IWRS) at a 1:1 ratio to:

- Study arm: subjects will be treated by Resolute Onyx stent

  OR

- Control arm: subjects will be treated by Resolute Integrity stent

The investigators will be required to verify that all inclusion and none of the exclusion criteria are met. To keep in line with the intent and spirit of the study, each lesion as stented will need to be given a single CASS site that best reflects its anatomical position. Medtronic will not consider this inconsistence to be a noncompliance.

Every effort will be tried to avoid potential bias. A randomized design has been chosen as the soundest method to compare two treatment options. Due to the similar design characteristics of the devices, the study investigators and operators cannot be blinded, the subjects will also not be blinded. However to ensure the integrity of the study outcomes, angiograms will be reviewed by an independent angiographic core lab and the event adjudication will be conducted by an independent clinical event committee (CEC), consisting of cardiologists who are not participating in the study.

The study flowchart is shown in Figure 6-1.

6.1. Duration

The enrollment period is anticipated to be approximately 11 months. Subjects will remain in the study and continue with baseline, 1 month, 6 months, 9 months and annual follow-up assessments until the final study assessment (i.e. 5-year assessment), study exit, or death, whichever comes first. Consequently, the entire study duration from enrollment to 5-year follow-up completion is anticipated to be approximately 71 months.

6.2. Rationale

The purpose of this study is to evaluate the clinical safety and efficacy of the Resolute Onyx stent(s), compared to the Resolute Integrity stent(s) implanted in subjects in China. This study is conducted to provide evidence in Chinese subjects confirming the clinical safety and efficacy of Resolute Onyx stent which has already been demonstrated in other populations outside of China. The study design is based on the CFDA DES clinical study guideline (draft

version for public comments). The data will be submitted to CFDA for Resolute Onyx product registration approval.

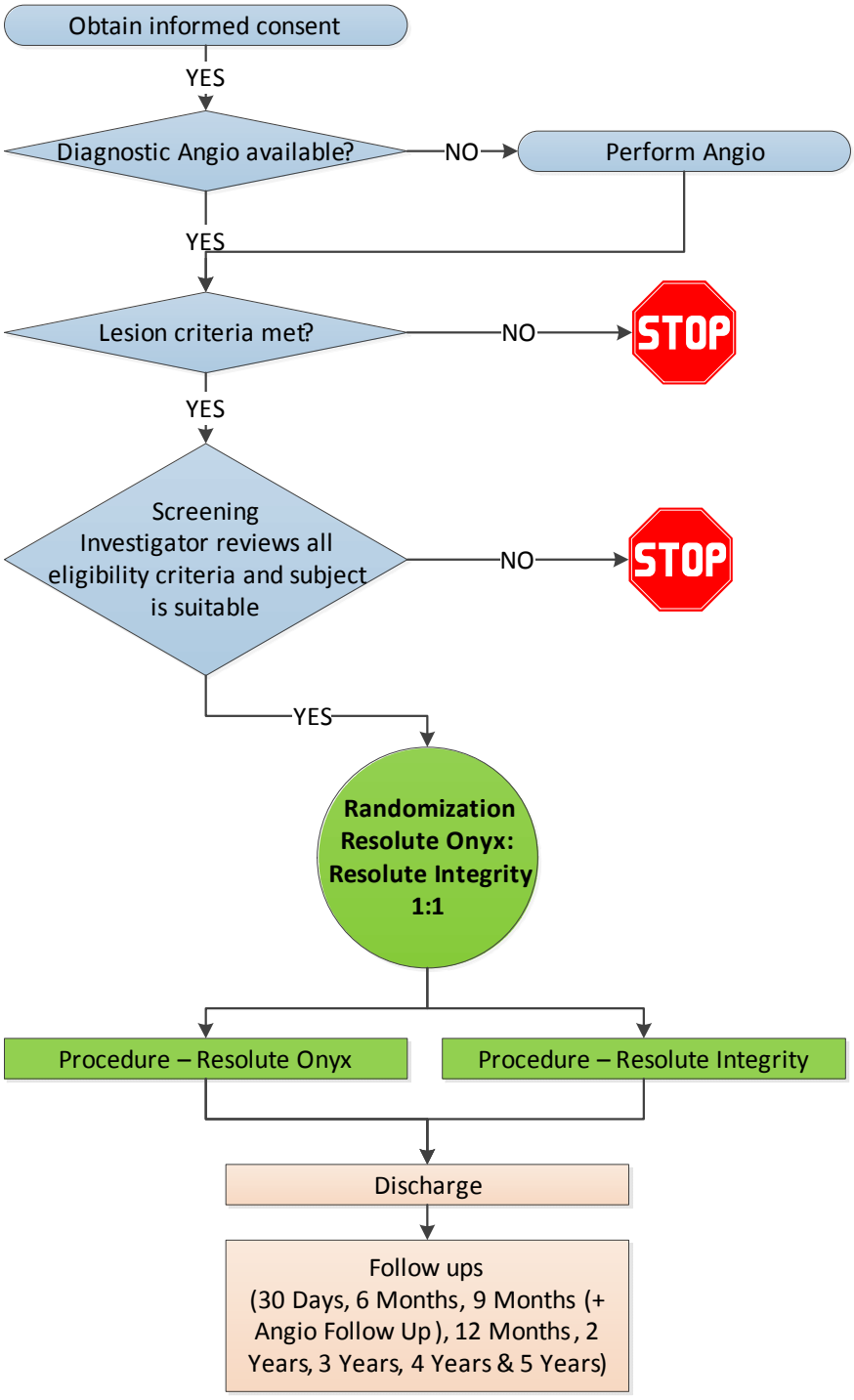


Figure 6-1 Study Flow Chart

7. Product Description

7.1. Study Device Name and Description

7.1.1. Study Arm - Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (Resolute Onyx Stent System) consists of four components:

1. Resolute Onyx™ Bare Metal Stent– a premounted cobalt alloy and platinum-iridium alloy based stent
2. Delivery System – Resolute Onyx™ Rapid Exchange (RX) Delivery System
3. Polymer System - BioLinx™ Polymer System
4. Zotarolimus – Anti-proliferative drug component/active pharmaceutical ingredient

Resolute Onyx is the next iteration of the Resolute family of products and utilizes the identical Resolute coating system (zotarolimus drug substance, BioLinx polymer, and drug dose density) as all predicate products within the Resolute portfolio. The product consists of the Onyx stent platform, Resolute coating system and next generation Onyx stent delivery system.

The Resolute Onyx stent is an iterative design update to the commercially available Resolute Integrity stent and utilizes the same continuous sinusoid manufacturing technology, with slight modifications to stent geometry incorporated to provide a lower crossing profile and thus improved deliverability over predicate products. The stent is manufactured from a composite wire which has an outer shell and an inner core. The following sections describe the constituent components of the Resolute Onyx product.

7.1.1.1. Resolute Onyx Stent Platform

Resolute Onyx utilizes the Onyx bare metal stent which is manufactured from a composite wire which has an outer shell and an inner core. The outer shell 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. A pictorial representation of the Resolute Onyx stent materials compared to the predicate, Resolute Integrity, is provided in Figure 7-1. The stent design has been modified slightly to provide a lower crossing profile and thus, improved deliverability over predicate products. A pictorial representation of the Resolute Onyx stent compared to the predicate, previous generation of Resolute Integrity is provided in Figure 7-2.

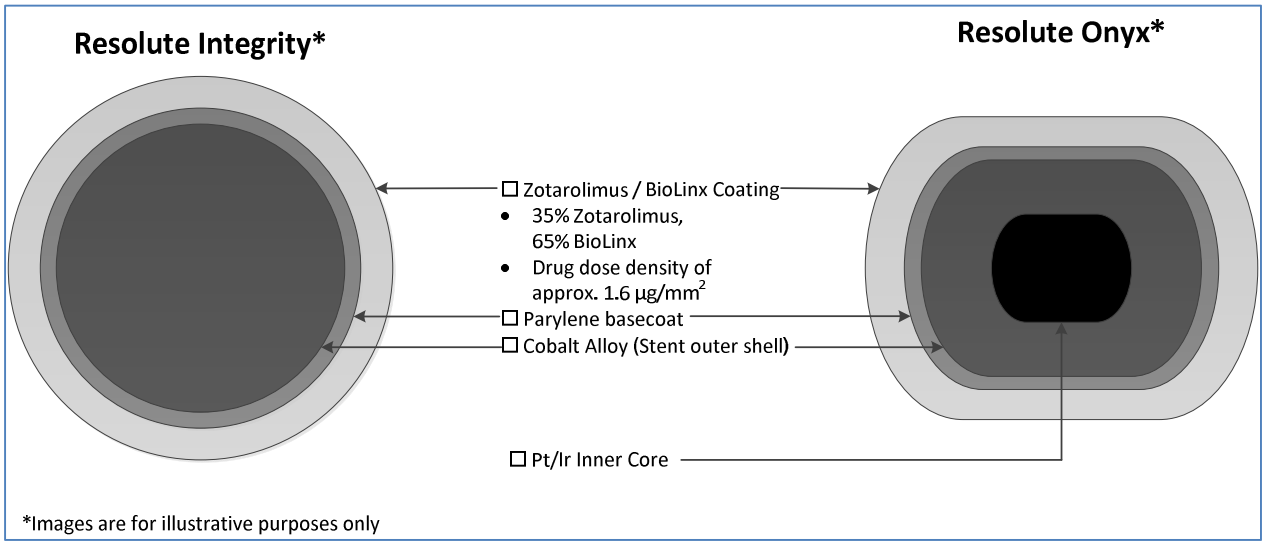


Figure 7-1 Resolute Integrity and Resolute Onyx Stent Materials

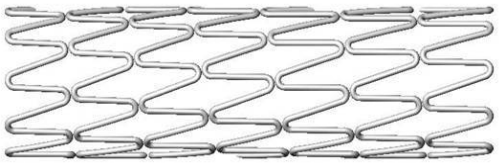
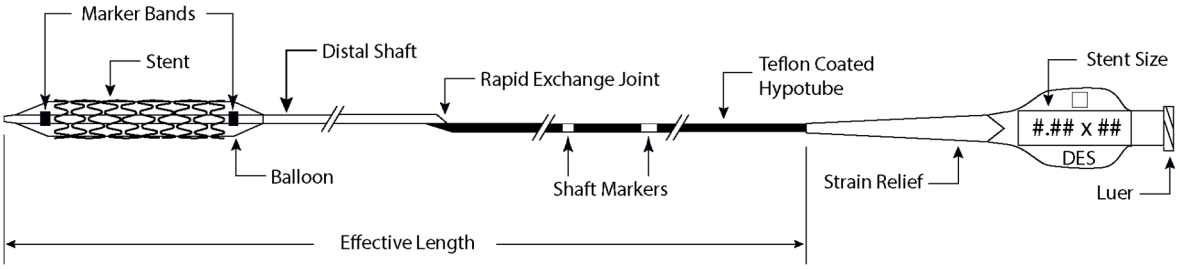
Resolute Integrity Stent	
Resolute Onyx Stent	

Figure 7-2 Resolute Integrity and Resolute Onyx Stent Design

7.1.1.2. Resolute Onyx Delivery System

The delivery system consists of a balloon-expandable intracoronary stent premounted on the Resolute Onyx™ Rapid Exchange (RX) delivery system with a catheter effective working length of 140 cm. The delivery system is compatible with 0.36 mm (0.014 in) maximum outer diameter guidewires and 1.42 mm (5 Fr/0.056 in) minimum inner diameter guide catheters. A graphic representation of the Onyx Rapid Exchange (RX) delivery system is presented in Figure 7-3.



Components Not Shown:
Hypotube stiffening wire
Inner Shaft (Inner Member)

Figure 7-3 Onyx RX Delivery System with Stent

7.1.1.3. Polymer System

Resolute Onyx stent employs the identical BioLinx polymer coating as its predicate Resolute products. The BioLinx polymer is the carrier for the drug substance, zotarolimus, and provides an extended elution profile for the finished product.

7.1.1.4. Drug-Zotarolimus

The drug zotarolimus is a proprietary chemical entity licensed from Abbott Laboratories. Zotarolimus is a tetrazole-containing macrocyclic drug. This component remains unchanged from the approved predicate Resolute products. The suggested mechanism of action of zotarolimus is to bind to FKBP-12, 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. Resolute Onyx utilizes a drug dose density of approximately 1.6 μg/mm^2 of stent surface area, which is identical to the drug dose density used for the approved predicate Resolute products. The total drug content (per stent) is determined by both drug dose density and stent surface area. The active drug Zotarolimus is intended to reduce the incidence of restenosis in coronary interventions.

7.1.2. Control Arm - Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System

The Medtronic Resolute Integrity Stent System consists of four components:

1. Integrity Bare Metal Stent – a pre-mounted cobalt alloy based stent
2. Delivery System – MicroTrac Rapid Exchange (RX) Delivery system
3. Polymer system - BioLinx™ Polymer System
4. Zotarolimus –Anti-proliferative drug component/active pharmaceutical ingredient

The Integrity stent is a result of manufacturing process modifications and optimizations to the approved Driver and Micro-Driver coronary stent platform. The primary modification is a change to the method of forming the stent sinusoidal architecture. The Integrity stent is manufactured from a cobalt alloy as the Driver stent. To create the Integrity stent, a single cobalt alloy wire is formed into a continuous sinusoidal pattern of crowns and struts which are then wound around a mandrel (see Figure 7-2).

7.1.2.1. MicroTrac Delivery System

The Resolute Integrity stent utilizes the MicroTrac delivery system design which has been approved by CFDA in the core sizes of Resolute Integrity™ Zotarolimus-Eluting Coronary stent system.

The Resolute Integrity stent is pre-mounted on a custom MicroTrac Stent Delivery System on a rapid exchange (RX) catheter with a balloon (See Figure 7-3). The balloon delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy. The delivery system is compatible with 0.014" (0.36 mm) guidewires and has an effective length of 140 cm.

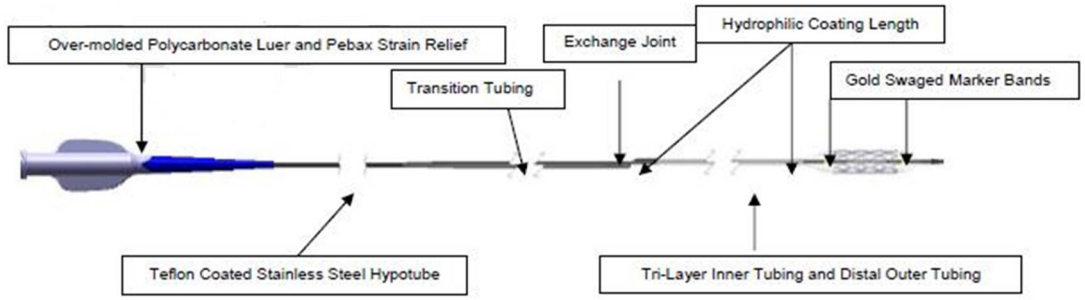


Figure 7-4 MicroTrac RX (Delivery System and Resolute Integrity Stent)

The distal end of the catheter shaft, proximal to the balloon, contains a guidewire entry port, providing the RX feature of this device. The proximal end of the catheter contains a luer adapter for balloon inflation and deflation.

7.1.2.2. Polymer System and Drug-Zotarolimus

The same as those in the Resolute Onyx stent system.

More detailed information of the products, including indications for use, contraindications, warnings and precautions, preclinical testing and materials in contact with tissues or body fluids, how supplied including storage and other information can be found in the Investigators' Brochure (IB) and/or 'Instructions for Use' (IFU).

7.2. Device Model and Labelling

Both stent systems will be labeled according to local labelling requirements in Chinese and indicated for clinical trial use only.

Table 7-1 Stent Model Number and Size of Resolute Onyx

Stent Name	Stent Diameter (mm)	Stent Length (mm)	Stent Model Number (CFN)
Resolute Onyx	2.25	8	RONYX22508X
Resolute Onyx	2.25	12	RONYX22512X
Resolute Onyx	2.25	15	RONYX22515X
Resolute Onyx	2.25	18	RONYX22518X

Stent Name	Stent Diameter (mm)	Stent Length (mm)	Stent Model Number (CFN)
Resolute Onyx	2.25	22	RONYX22522X
Resolute Onyx	2.25	26	RONYX22526X
Resolute Onyx	2.25	30	RONYX22530X
Resolute Onyx	2.5	8	RONYX25008X
Resolute Onyx	2.5	12	RONYX25012X
Resolute Onyx	2.5	15	RONYX25015X
Resolute Onyx	2.5	18	RONYX25018X
Resolute Onyx	2.5	22	RONYX25022X
Resolute Onyx	2.5	26	RONYX25026X
Resolute Onyx	2.5	30	RONYX25030X
Resolute Onyx	2.75	8	RONYX27508X
Resolute Onyx	2.75	12	RONYX27512X
Resolute Onyx	2.75	15	RONYX27515X
Resolute Onyx	2.75	18	RONYX27518X
Resolute Onyx	2.75	22	RONYX27522X
Resolute Onyx	2.75	26	RONYX27526X
Resolute Onyx	2.75	30	RONYX27530X
Resolute Onyx	3	8	RONYX30008X
Resolute Onyx	3	12	RONYX30012X
Resolute Onyx	3	15	RONYX30015X
Resolute Onyx	3	18	RONYX30018X
Resolute Onyx	3	22	RONYX30022X
Resolute Onyx	3	26	RONYX30026X
Resolute Onyx	3	30	RONYX30030X
Resolute Onyx	3.5	8	RONYX35008X
Resolute Onyx	3.5	12	RONYX35012X
Resolute Onyx	3.5	15	RONYX35015X
Resolute Onyx	3.5	18	RONYX35018X
Resolute Onyx	3.5	22	RONYX35022X
Resolute Onyx	3.5	26	RONYX35026X
Resolute Onyx	3.5	30	RONYX35030X
Resolute Onyx	4	8	RONYX40008X
Resolute Onyx	4	12	RONYX40012X
Resolute Onyx	4	15	RONYX40015X
Resolute Onyx	4	18	RONYX40018X
Resolute Onyx	4	22	RONYX40022X
Resolute Onyx	4	26	RONYX40026X

Stent Name	Stent Diameter (mm)	Stent Length (mm)	Stent Model Number (CFN)
Resolute Onyx	4	30	RONYX40030X

Table 7-2 Stent Model Number and Size of Resolute Integrity

Stent Name	Stent Diameter (mm)	Stent Length (mm)	Stent Model Number (CFN)
Resolute Integrity	2.25	8	RSINT22508X
Resolute Integrity	2.25	12	RSINT22512X
Resolute Integrity	2.25	14	RSINT22514X
Resolute Integrity	2.25	18	RSINT22518X
Resolute Integrity	2.25	22	RSINT22522X
Resolute Integrity	2.25	26	RSINT22526X
Resolute Integrity	2.25	30	RSINT22530X
Resolute Integrity	2.5	8	RSINT25008X
Resolute Integrity	2.5	12	RSINT25012X
Resolute Integrity	2.5	14	RSINT25014X
Resolute Integrity	2.5	18	RSINT25018X
Resolute Integrity	2.5	22	RSINT25022X
Resolute Integrity	2.5	26	RSINT25026X
Resolute Integrity	2.5	30	RSINT25030X
Resolute Integrity	2.75	8	RSINT27508X
Resolute Integrity	2.75	12	RSINT27512X
Resolute Integrity	2.75	14	RSINT27514X
Resolute Integrity	2.75	18	RSINT27518X
Resolute Integrity	2.75	22	RSINT27522X
Resolute Integrity	2.75	26	RSINT27526X
Resolute Integrity	2.75	30	RSINT27530X
Resolute Integrity	3	9	RSINT30009X
Resolute Integrity	3	12	RSINT30012X
Resolute Integrity	3	15	RSINT30015X
Resolute Integrity	3	18	RSINT30018X
Resolute Integrity	3	22	RSINT30022X
Resolute Integrity	3	26	RSINT30026X
Resolute Integrity	3	30	RSINT30030X
Resolute Integrity	3.5	9	RSINT35009X
Resolute Integrity	3.5	12	RSINT35012X
Resolute Integrity	3.5	15	RSINT35015X
Resolute Integrity	3.5	18	RSINT35018X

Stent Name	Stent Diameter (mm)	Stent Length (mm)	Stent Model Number (CFN)
Resolute Integrity	3.5	22	RSINT35022X
Resolute Integrity	3.5	26	RSINT35026X
Resolute Integrity	3.5	30	RSINT35030X
Resolute Integrity	4	9	RSINT40009X
Resolute Integrity	4	12	RSINT40012X
Resolute Integrity	4	15	RSINT40015X
Resolute Integrity	4	18	RSINT40018X
Resolute Integrity	4	22	RSINT40022X
Resolute Integrity	4	26	RSINT40026X
Resolute Integrity	4	30	RSINT40030X

7.3. Intended Use

The Resolute Onyx Stent System (investigational) and Resolute Integrity Stent System (control) are intended to improve coronary luminal diameters in subjects with symptomatic ischemic heart disease due to stenotic lesion(s) amenable to treatment with stents' diameter from 2.25 mm to 4.0 mm and stents' length from 8 mm to 30 mm. The stents are intended as permanently implanted devices.

7.4. Probability analysis of success

The manufacturing system of Medtronic has been tested and proven for many years. The quality of the investigational device has been carefully examined and verified before delivery. The investigational device has been commercially available globally, including the Europe and many other countries, with a certain number of clinical application or post-marketing follow-up. The basic principles, structure composition and materials etc. comply with the international and domestic standards, or has been carefully examined and verified by Medtronic, as well as tested, qualified by CFDA certificated medical device testing organization. The study design of this study complies with related CFDA instructions and requirements of ethical review, and all potential subjects will be strictly selected according to indications of the investigational device.

7.5. Probability analysis of failure

Although regulatory/ethical/scientific and medical requirements have been fully taken into consideration, the unanticipated risk in the clinical application of investigational device could lead to failure of this study. Potential risks could be reduced with well-trained study staff and strict protocol compliance.

8. Selection of Subjects

8.1. Study Population

Those who are eligible for PTCA in *de novo* lesions amenable to treatment with either Resolute Onyx or Resolute Integrity stent systems will be the target study population in China. Approximately 550 subjects from approximately 20 sites who meet the eligibility criteria and sign the informed consent form will participate in this study.

8.2. Subject Enrollment

All subjects presenting to the cardiac catheterization laboratory for possible interventional treatment are potential candidates. Subjects who do not meet all inclusion criteria or meet any one of the exclusion criteria will not be enrolled to participate in the clinical study. For details of the point of enrollment, refer to section 9.5.3.

8.3. Inclusion Criteria

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

8.3.1. General Inclusion Criteria:

1. Subject is ≥ 18 years old
2. The subject is an acceptable candidate for treatment with a drug-eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions, the Investigator Brochure (IB) of Resolute Onyx™ stent, and the Instructions for Use (IFU) of Resolute Integrity™ stent
3. The subject has been informed of the nature of the study and has consented for the subject to participate and authorized the collection and release of his/her medical information by signing an Informed Consent Form
4. Intention to follow randomization for implanting at least one Resolute Onyx stent or one Resolute Integrity stent
5. Subject agrees to have all study procedures performed, and is willing to comply with all protocol-required evaluations and to return to the same investigational site where the procedure was performed for follow up angiography

8.3.2. Angiographic Inclusion Criteria (visual estimate):

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

6. The subject requires treatment of up to 3 target lesions in up to 2 separate target vessels [2 target lesions in 1 vessel (including its side branches) and 1 target lesion in a separate vessel (including its side branches)] amenable to treatment with stents with diameter from 2.25 mm to 4.0 mm
7. Target lesion must be de novo lesion located in a native coronary artery, with the visually estimated target reference vessel diameter (RVD) and lesion length eligible for treatment by the stent size ranges shown in Table 8-1 Resolute Onyx™ Stent Size Matrix or Table 8-2 Resolute Integrity™ Stent Size Matrix

Table 8-1 Study Arm (Resolute Onyx™ Stent Size Matrix)

Stent Diameter (mm)	Stent Length (mm)						
	8	12	15	18	22	26	30
2.25	●	●	●	●	●	●	●
2.5	●	●	●	●	●	●	●
2.75	●	●	●	●	●	●	●
3.0	●	●	●	●	●	●	●
3.5	●	●	●	●	●	●	●
4.0	●	●	●	●	●	●	●

Table 8-2 **Control Arm (Resolute Integrity™ Stent Size Matrix)**

Stent Diameter (mm)	Stent Length (mm)								
	8	9	12	14	15	18	22	26	30
2.25	●	-	●	●	-	●	●	●	●
2.5	●	-	●	●	-	●	●	●	●
2.75	●	-	●	●	-	●	●	●	●
3.0	-	●	●	-	●	●	●	●	●
3.5	-	●	●	-	●	●	●	●	●
4.0	-	●	●	-	●	●	●	●	●

8. Target lesion must have visually estimated stenosis ≥ 50%
9. Target vessel must have a thrombolysis in myocardial infarction (TIMI) flow ≥ 2

8.4. Exclusion Criteria

8.4.1. General Exclusion Criteria

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

1. Known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, P2Y12 inhibitors, 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 STEMI within 24 hours prior to index 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) elevation of 2mm from baseline 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 motion abnormality

Note: Subjects with evidence or suspicion of an acute MI (per Investigator or Sub-Investigator determination) must have cardiac biomarker values reviewed prior to enrollment

6. Any previous treatment of the target lesion, including but not limited to previous PTCA, or an in-stent restenosis (ISR) lesion
7. Any staged PCI of any vessel at any time post index procedure
8. Documented left ventricular ejection fraction (LVEF) < 30% at the most recent evaluation prior to index procedure
9. Previous percutaneous coronary intervention (PCI) of the target vessel within 9 months prior to the procedure

Note: Refer to Table 8-3 in Section 8.4.3 for criteria of previous PCI of the target and other (non- target) vessel(s)

10. During the index procedure, the target lesion 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.)
11. History of a stroke or transient ischemic attack (TIA) within the prior 6 months
12. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months
13. History of bleeding diathesis or coagulopathy or will refuse blood transfusions
14. Concurrent medical condition with a life expectancy of less than 12 months
15. 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
16. Inability to comply with the required trial antiplatelet regimen
17. A woman who is pregnant, lactating or planning to be pregnant within 12 months after index procedure

8.4.2. Angiographic Exclusion Criteria

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

18. Target lesion is in a bypass graft, including but not limited to saphenous vein graft (SVG) or a left/right internal mammary artery (LIMA/RIMA)

19. Unprotected left main coronary artery disease (no patent bypass graft(s) to one or more branches of the left coronary artery; the left anterior descending or circumflex artery, with an obstruction greater than 50% in the left main coronary artery)
20. TIMI flow is 0 (including but not limited to CTO lesions)
21. Planned two stent treatment for bifurcated lesions (bifurcated lesions treated with provisional stenting is allowed)
22. Previous stenting in the target vessel that: within 9 months prior to procedure; or previous stenting in the target vessel ≤ 15 mm from the target lesion
23. The target vessel has evidence of thrombus

8.4.3. Criteria for Additional Procedures

Table 8-3 Previous and Additional Procedure Criteria

Prior to Index Procedure		
Time Point	Target Vessel(s)	Non-Target Vessel(s)
> 9 months pre-index	Any approved treatment, provided: -Target lesion must be at least 15 mm away from a previously placed stent or treatment	Any approved treatment
9 months to > 30 days pre- index	No PCI	Any approved treatment
30 days to index	No PCI	No PCI
Post Index Procedure		
- No planned/staged PCI at any time post index procedure. - If deemed medically necessary by investigator, the subjects should receive any necessary treatment, but any interventional or surgical treatment to coronary artery lesions post index procedure (including but not limited to PCI and/or CABG) should be reported as revascularization events		

9. Study Procedures

9.1. Schedule of Events

Table 9-1 Schedule of Treatments and Assessments

Event	Index Hospitalization					Follow up Assessments		
	Screen/Pre-procedure			Procedure	Post-Procedure[1]	30-day 6-month	9-month	1-5 years annually
	Screen	Prior to procedure within 7 days	Prior to procedure within 72 hrs.			Subject Contact[2]	Angio Follow up	Subject Contact[2]
Informed Consent	●							
Demographics	●							
Medical and cardiac history	●							
Cardiac risk factors	●							
Current cardiac status	●							
Angina Status	●				●	●	●	●
White Blood Cell		●						
Platelet Count		●						
Serum creatinine		●						
Pregnancy Test[3]		●						
Cardiac biomarkers[4]			●		●1st: ≥3hrs;2nd: >4 hrs. after 1st and < 24 hrs.			
12-lead ECG[5]		●			●			
LVEF[6]	●							
Eligibility	●	●	●	●				
Procedure data				●				
Angiogram[7]				●			●	
AE and SAE[8]	●	●	●	●	●	●	●	●
ConcomitantMedication[9]	●	●	●	●	●	●	●	●

1. End of procedure is defined as removal of the guide catheter
2. Subject contact includes phone call, mail, email or clinical visit
3. Only required for no-menopause women subjects
4. Cardiac biomarkers will be collected pre-procedure within 72 hours and post-procedure at two time points: the first collection should occur 3 or more hours post-procedure and the second collection should occur 4 hours after the first collection but prior to 24 hours. It is preferred to collect CK and another biomarker e.g. CK-MB and/ or Troponin:
   - Preferred: "CK and CK-MB" or "CK and Troponin" or "CK, CK-MB and Troponin"
   - Unacceptable: "CK" values alone (will treat CK value alone as protocol deviation)
   - If a Myocardial Infarction has occurred after procedure or during study period, CK and CK-MB or CK and Troponin values will be collected. If any CK elevation (CK above upper limit of normal) is noted post-procedure, CK and CK-MB or CK and Troponin measurements will continue to be performed per local hospital practice starting from when the first elevation is noted until return of levels towards normal or discharge and recorded on the appropriate CRF
5. A 12 lead ECG will be performed within 7 days prior to the procedure and within 24 hours post-procedure or at discharge whichever comes first. Relevant copies of ECGs will be collected for death or any (suspected) myocardial infarction or (suspected) stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Events Committee (CEC). This includes copies of the baseline ECG (pre- and post-index procedure and discharge) and event ECG (most abnormal ECG and last ECG recorded) if available
6. A LVEF value within the last 6 months pre-procedure is acceptable
7. For subjects for death or any (suspected) myocardial infarction or (suspected) stent thrombosis that occurs after the index procedure, all baseline, procedural, 9 months follow-up (if applicable) and event angiograms will be collected. The angiograms will be reviewed by an independent angiographic core lab
8. All AE information (e.g. AEs and SAEs) will be documented from the date the informed Consent From (ICF) signed until the 5-year follow-up assessment
9. Only anti-platelet and anti-coagulation medication will be collected as concomitant medication from the date the ICF signed until the 5-year follow-up assessment

9.2. Subject Screening

All subjects admitted for potential PCI of the coronary arteries are the targeted study population. Subjects who signed the Informed Consent Form (ICF) and meet all eligibility criteria will continue the next study processes

9.3. Subject Consent

9.3.1. Consent

Written informed consent must be obtained prior to subject participation in any study related activity. Subjects should receive the EC approved ICF well in advance of the consent discussion. During the consent discussion, the investigator or his/her designee must fully inform the subject of all pertinent aspects of the study that are relevant to a subject's decision to participate in the clinical study. If a subject is illiterate, an impartial witness must be present during the entire informed consent discussion. All items discussed in the ICF must be explained. The language used shall be in the subject's native language, as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject. The informed consent process shall be documented before any procedure specific to the clinical study is applied.

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 study. The informed consent process shall not appear to waive the subject's rights.

It is anticipated that some patients may sign a consent form and later be found to be ineligible due to angiographic criteria. Such patients are not considered part of the study endpoint analysis population.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given. Signing the ICF serves to document the written and verbal information that the investigator or authorized delegate provides to the subject, the subject's understanding of the information, and their agreement to participate. After all persons have signed and dated the ICF, the investigator must provide the subject with a copy of the signed and dated ICF. The original signed consent form will be retained in the subject's study records.

No patients from a vulnerable population will be included into the study. In addition, due to the nature of the eligibility criteria of the study, waiver of prior informed consent process due to emergency treatments is not applicable in this study.

9.3.2. Revision for Informed Consent Form

As directed by the regulatory authorities, EC or Medtronic, subjects may have to be re-consented to new revisions of the informed consent throughout the duration of the study.

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

Medtronic will revise the written ICF whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the investigator for EC approval. After approval by the EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

9.4. Randomization and Treatment Assignment

After written informed consent has been obtained, all of the inclusion and none of the exclusion criteria have been met, and prior to percutaneous coronary intervention, subjects will be randomized using an interactive web response system (IWRS). Randomization will be performed at 1:1 ratio to the study arm or control arm. As described in section 6, investigators, operators and subjects will not be blinded.

Subjects will be randomized to one of the following two groups:

- Study group - Treatment with Medtronic Resolute Onyx Stent System (Table 8-1)
- Control group - Treatment with Medtronic Resolute Integrity Stent System (Table 8-2)

If by mistake a subject is randomized twice or more, the first assigned treatment arm will be used for the intention-to-treat analysis, and investigators should treat subjects accordingly. The subjects who are assigned to Resolute Onyx Stent System treatment group should only be treated with the Resolute Onyx Stent System. The subjects who are assigned to Resolute Integrity Stent System treatment group should only be treated with the Resolute Integrity Stent System. If the assigned stents were not used, this will be reported as protocol deviation.

Randomization will be documented on electronic CRFs. Due to the "open" nature of this study, it is important to prevent selection bias. Since knowledge of the randomization procedure may lead to selection bias, the randomization procedure therefore will be described in a separate document.

9.5. Procedures

Subject preparation and treatment of the target lesion(s) will be performed in accordance with the hospital's standard policies and procedures for care of the interventional cardiology patients unless otherwise specified in this Investigation Plan.

The stenting procedure should be performed according to the IB for the Resolute Onyx stent, IFU for the Resolute Integrity stent and the Angiographic Core Lab procedures in Appendix 3.

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 Resolute Onyx stent IB or Resolute Integrity Stent IFU as applicable.

9.5.1. 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.

   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 3).

9.5.2. Target Lesion Pre-treatment

The target lesion(s) will be pre-treated in accordance with IB for Resolute Onyx stent and the IFU of Resolute Integrity. The use of other pre-treatment (e.g., cutting balloons, atherectomy, laser, thrombectomy, etc.) is not allowed.

9.5.3. Point of Enrollment

Based on the review of available information, all patients who are deemed to be a potential candidate for the study will be asked to participate. The point of enrollment is the moment of randomization.

Per full analysis set (FAS) principles, subjects who did not have a study stent implanted but a study stent was introduced into the guide catheter will be followed through 12 months for clinical assessments. Since analysis will be performed according to the FAS principle, subjects, who went through the randomization but did not have study stent implanted due to reasons such as delivery failure of one of more study stents, should be included and followed up until 12 months clinical follow up finished. In cases where the procedure was stopped prior to the study stent being delivered into the guide catheter (e.g. subject became unstable, power outage, equipment issues, etc.), the subject will not participate or be followed in the clinical study. No replacement will be done for randomization.

All reportable events occurring after the randomization, irrespective of whether the stent implantation procedure has actually started, must be documented in the electronic Case Report Form (eCRF).

Subject enrollment and stent use information will be submitted to Medtronic on the eCRF within 10 business days or as soon as source documents are available. Subject screening and enrolment will be documented in subject identification log and screening log as appropriate.

9.5.4. Stenting Procedure

The stenting procedure should be performed according to the IB for Resolute Onyx and IFU for Resolute Integrity.

Stent length(s) should be selected so that the lesion can be fully covered. 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 and the stent length (single stent or after overlapping if multiple stents) must be ≥ 3 mm longer than the lesion length.

For subjects with multiple target lesions, the first lesion must be treated successfully and the subject must be clinically stable before treatment of the following lesion(s) is attempted.

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

Successful treatment of the lesion is defined as:

1. <10% residual diameter stenosis result is achieved (visual assessment)
2. TIMI 3 flow is present post treatment
3. 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 study 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 and will be considered a protocol deviation.

9.5.4.1. 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 study stents may be employed as a bailout treatment.

In this trial, it is recommended that each target lesion to be covered with a single stent. If overlapping is necessary, it is recommended to overlap the study stents for 3 mm to avoid the potential for gap restenosis. If incomplete coverage occurs during the procedure, additional stenting with study stents may be employed to provide complete coverage.

9.5.4.2. Treatment Failure

A study stent that enters the guide catheter but fails to be implanted at the intended location will be recorded in the eCRF. In the event of a failure to implant at least one study device, the Investigator may choose to treat the target lesion(s) with any approved device.

Note: There are no clinical data available regarding the interaction of the Resolute Onyx stent or Resolute Integrity stent implanted in the vicinity of other types of drug-eluting stents. Damaged or failed Resolute Onyx or Resolute Integrity stent(s) (including ancillary devices) must be returned to Medtronic per related instructions in Medtronic SOP.

9.5.5. 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 3).

The end of the procedure is defined as the time the last 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.

Adverse events that occur during the procedure must be recorded on the CRF.

9.5.6. Post-procedure to Hospital Discharge

For post-procedure 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.

Qualified study staff at the investigational site will assess the subject's clinical status (including angina) prior to discharge and record any adverse events.

9.6. Medication Compliance

The following anti-platelet therapy is strongly recommended for index procedure:

Aspirin: 75 mg daily for 3 days prior to the procedure, or a peri-procedural loading dose between 250-500 mg.

Approved P2Y12 inhibitor medications: (i.e. Clopidogrel: 75 mg for 3 days prior to the procedure or a pre-procedural loading dose between 300-600 mg).

Following the procedure, Aspirin (at least 75 mg daily) should be continued indefinitely. Approved P2Y12 inhibitors (i.e. Clopidogrel) should be prescribed for at least 6 months in stable ischemic heart disease subjects and for at least 12 months in subjects with acute coronary syndrome (ACS)as per ACC/AHA/SCAI guidelines

All other co-medication usage is at the Investigators discretion and should be done according to hospital routine.

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 resumed as soon as possible, per the discretion of their treating physicians.

9.7. Assessment of Efficacy

Efficacy will be evaluated by the status of primary endpoint and secondary endpoints related with efficacy.

9.8. Assessment of Safety

Safety will be evaluated by the safety related endpoints, and reported AE and SAE data.

9.9. Recording Data

9.9.1. Follow-up

Follow-up assessments will be done at the intervals listed in Table 9-2:

Table 9-2 Schedule of Treatments and Assessments

Follow-up Interval	Window	Method
30 Days	± 5 days	Contact*
6 Months	±14 days	Contact

9 Months	± 30 days	Clinic Visit
12 Months	±30 days	Contact
2 Years	± 30 days	Contact
3 Years	± 30 days	Contact
4 Years	± 30 days	Contact
5 Years	± 30 days	Contact

*Subject contact includes phone call, email or clinic visit

Except for subjects who are required to undergo the 9-month follow-up angiography, the follow-ups at other time points can be done by phone or preferably by outpatient clinic visit.

The 9-month follow-up includes clinical assessment and an angiography. Clinical assessments (e.g. angina status, verifying adverse events) must be performed prior to the angiography. If a patient has a repeat angiogram prior to the 9 months visit and the target lesion is not visualized, angiography must be performed at the 9-month visit. If a patient has a repeat angiogram prior to the 9-month follow-up visit and the target lesion is visualized, the requirements for 9-month angiogram are provided in Table 9-3.

Table 9-3 Repeat Angiographic Follow-up

Post-Procedure Angiographic Time Point	Target Lesion Revascularization Performed?	Angiography Required at 9 months?
< 30 days post-procedure	Yes	Yes
	No	Yes
⩾ 30 days post-procedure	Yes	No
30 days to 5 months post-procedure	No	Yes
> 5 months post procedure	No	No

Note: compliance to the follow-up schedule is essential to enable an analysis of the results in a scientifically sound and meaningful way. If, for whatever reason, the subject follow-up cannot be scheduled within the time window or occurred outside the time window, it is still essential to document the subject data at a date as close as possible to the calculated follow-up date. 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's follow-up compliance. At every follow-up assessment the study site research personnel should try to contact the subject.

Table 9-1 in section 9.1 summarizes what data will be collected prospectively within this study.

9.9.1.1. ECG

A 12-lead electrocardiogram (ECG) will be performed within 7 days prior to the procedure and within 24 hours post-procedure or prior to discharge whichever comes first. For events that occur after the index procedure and are related to a study endpoint including but not limited to death, (suspected) myocardial infarction or stent thrombosis events, event ECG

printouts will be collected for adjudication purposes by an independent Clinical Events Committee (CEC).

9.9.1.2. Angiography

There is a mandatory angiographic follow-up at 9 months post procedure for all subjects per study design. Visual estimation of lesion characteristics in relation to the index procedure will be done by the operator and core lab separately.

Baseline, procedural, 9-month angiographic follow-up and event angiograms will be collected that are related to a study primary or secondary endpoint, including but not limited to death, (suspected) myocardial infarction or stent thrombosis.

Furthermore, angiograms will be collected in cases of a delivery failure. All angiograms will be reviewed by an independent angiographic core lab.

9.9.1.3. Cardiac Biomarkers

Cardiac biomarkers will be collected pre-procedure within 72 hours and post-procedure at two time points: the first collection should occur 3 or more hours post-procedure and the second collection should occur 4 hours after the first collection but prior to 24 hours. It is preferred to collect CK and another biomarker e.g. CK-MB and/ or Troponin:

- Preferred: “CK and CK-MB” or “CK and Troponin” or “CK, CK-MB and Troponin”
- Unacceptable: “CK” values alone (will treat CK value alone as protocol deviation)

If a Myocardial Infarction has occurred after procedure or during study period, CK and CK-MB or CK and Troponin values will be collected. If any CK elevation (CK above upper limit of normal) is noted post-procedure, CK and CK-MB or CK and Troponin measurements will continue to be performed per local hospital practice starting from when the first elevation is noted until return of levels towards normal or discharge and recorded on the appropriate CRF.

9.9.1.4. Other Clinical Laboratory Procedures & Test

Please refer to Table 9-1.

9.9.1.5. Medication

The electronic CRF will have separate pages to capture data on concomitant medication information. The concomitant medication page will be limited to capture data on anti-platelet/anticoagulant medication.

9.9.1.6. Source document collection in case of events to be adjudicated by the CEC

For the purpose of adjudication of events by the Clinical Events Committee, relevant event related source documents will be collected for events that need to be adjudicated by the CEC. Refer to the CRF instructions for further details.

9.10. Deviation Handling

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the protocol or the Investigator agreement. The

investigator is not allowed to deviate from these documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation. Examples of protocol deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain EC approval before the start of the study
- Implanted subject did not meet inclusion/exclusion criteria
- Fail to treat subjects according to the randomization result
- Required testing and/or measurements not done or incorrectly done
- Unauthorized use of investigational devices
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of subjects during lapse of EC approval
- Enrollment limits exceeded

Investigators should obtain prior approval from Medtronic before initiating any change or deviation from the CIP, except where necessary to protect the life or physical wellbeing of a subject in an emergency situation. Such approval shall be documented in writing and maintained in the investigator site 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 check-up).

Deviations will be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations should be reported to Medtronic via the Study Deviation eCRF (1 eCRF for each protocol deviation per each subject). Relevant information for each deviation will be documented on a deviation form completed by site personnel and reviewed by the Investigator.

Investigators should report deviations to Medtronic and their reviewing EC in accordance with reporting requirements of local EC.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be warranted such as amending the CIP, in accordance with Medtronic SOPs. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, which may include suspension of enrollment or termination of the investigator's or site's participation in the study.

9.11. Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the study through the 5-year follow-up. However, it is acknowledged that subjects have the right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled or the

Investigator may deem study withdrawal an appropriate action for a given subject due to documented medical reasons.

Subjects will be included in the analyses up to the time that consent was withdrawn but they will not be replaced in the enrollment of total study subjects. If discontinuation is because of problems related to the study device, the subject shall be asked to be followed for collecting safety data outside the clinical investigation. In all other cases, no additional data will be captured after the subject withdraws or is removed from the study, unless the information is publicly available.

If a subject decides to withdraw from the study or is withdrawn / removed from the study, the investigator will document the reason for withdrawal and indicate any rationale for the withdrawal from the study in the subject's file. Examples of situations in which an investigator may withdraw a subject from the study include but are not limited to:

1. Subject routinely fails to complete required procedures
2. Medical necessity

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. Continuous attempts throughout the five-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 highly recommended to document each attempt to contact the subject and the method used (e.g. telephone contacts, registered letters) in the subject's records.

A study exit form is required for all subjects upon his or her completion of the study, regardless of the reason for study exit.

Subjects exiting the study will not receive any additional continued care as part of the study. Subjects will be treated according to standard of medical care (including the standard care specified for post PCI procedure) following exit from the study.

10. Risks and Benefits

The results of risk analysis, balancing benefits against risks associated with both the device system itself and procedures involved in its use, is included in the Resolute Onyx IB and Resolute Integrity IFU.

10.1. Potential Risks

For the detailed information on the risks of implantation of the Resolute Onyx stent or the Resolute Integrity stent, including a complete list of warnings, precautions and potential adverse events, refer to the Resolute Integrity IFU and the Resolute Onyx IB.

With the use of coronary stenting devices, IVUS (intravascular ultrasound), or PCI (percutaneous coronary intervention) here lists the potential adverse events in order of severity:

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

- Balloon rupture
- Stent migration
- Failure to deliver the stent
- Stent misplacement

The occurrence of the above listed complications may lead to the need for a repeat catheterization and/or percutaneous coronary intervention, myocardial infarction, emergency bypass surgery, or death. The following additional side effects/complications may be associated with, but not limited to, the use of zotarolimus:

- Anemia
- Circumoral paresthesia
- Diarrhea
- Dry skin
- Headache
- Hematuria
- Infection
- Pain (abdominal or arthralgia)
- Rash

The side effects/complications of the BioLinx polymer are no different than those of other stent coatings and may include, but are not limited to, the following:

- Focal inflammation at the site of stent implantation
- Restenosis of the stented artery
- Allergic reaction

Participation in this study also makes subjects be exposed to radiation from x-ray procedures. Whether or not participate the study, subjects will undergo a diagnostic angiography and/or index PCI procedure, during which they will be exposed to x-ray. What is extra requirement for subjects is the 9-month angiographic follow-up (if applicable). These tests or treatments involve a small amount of radiation, but it is necessary to guide the procedure or examination. The amount of radiation subjects is exposed to during this study will depend on the complexity of the procedure.

There may be other discomforts and risks related to the device and/or this study that are not foreseen at this time.

Standard risks associated with the medical device used in this study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices are listed in the IB.

The evaluation of risk associated with the Resolute Onyx Stent System and the Resolute Integrity Stent System was performed in accordance with ISO14971: 2012 and Medtronic internal requirements. Based on the analysis performed, the residual risks associated with each hazard/failure mode were deemed acceptable to allow for clinical evaluation.

The risks associated with using this device are those associated with standard percutaneous coronary diagnostic and treatment procedures. The additional risk of using this device is associated with the zotarolimus drug and BioLinx polymer coating.

The risks of the Resolute Onyx System and Resolute Integrity System 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.

10.2. Potential Benefits

Participation will provide subjects and treating physicians an additional treatment option with Medtronic's new generation DES (The Resolute Onyx stent), which has been approved in 89 other countries and regions around the world. Participation also contributes to expanding the knowledge base with respect to procedural and clinical outcomes of new coronary stents.

Moreover, investigator will provide up to 5 years' clinical follow up to subjects post procedure according to the CIP procedure, which means subjects will receive more regular health care and follow up than the standard care in China for those who do not participate in this study.

10.3. Risk-Benefit Rationale

For study arm Resolute Onyx, the pre-clinical data (including animal studies and other technical testing) suggest Resolute Onyx Stent System can be used safely and reliably for its intended purposes. Resolute Onyx stent had already been approved and widely used in 89 countries or regions around the world already, including EU.

Risks associated with using the Resolute Onyx stent are similar to those associated with any other approved drug-eluting coronary stent (DES) used during percutaneous coronary interventional procedures.

For control arm Resolute Integrity, it is a CFDA approved product. So the risks are also similar to using any other approved DES.

Compared with eligible patients who receive routine hospital care (any approved DES) and do not participate in this study, subjects will have very limited extra risks than using any approved DES.

All efforts will be made to minimize the risks in the study by selecting Investigators who are experienced and skilled in interventional procedures including stenting, by training implanting physicians on the IB and IFU prior to the study start at each site, by clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled, by ensuring that treatment and check-up of the subject are consistent with current medical practices, and by an independent CEC which will review endpoint-related adverse events in order to advise Medtronic regarding study conduct should safety concerns be identified.

10.4. Liability

Subjects do not need to pay for the investigational devices (including study arm device and control arm device). Moreover, the 9 months angiographic follow up procedure cost does not require subjects to pay.

The free device, free angiographic examine at 9 months post procedure and a more regular clinical health care post procedure provided in this study are reasonable and can overweigh the risks.

10.5. Alternatives

Presently, therapeutic alternatives for subjects with the clinical indication targeted for the Resolute Onyx stent system and Resolute Integrity stent system range through the following:

- Other commercially available stent system with a drug or without drug
- Balloon angioplasty
- CABG
- Medical treatment

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

The definitions to be applied for the purposes of reporting adverse events are provided in Table 11-1.

Table 11-1 Adverse event definitions for reporting requirements

Event Type	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *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.* *(ISO 14155:2011[5] section 3.2)*
	The medical events with disadvantages occurred during the clinical study, no matter whether they are related to investigational medical devices or not. *(Good Clinical Practice for Medical Devices (CFDA Order No.25) -Article 93)*
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

[5] International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects – Good Clinical Practice.

Event Type	Definition
	NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. *(ISO 14155:2011 section 3.37)*
	Any untoward medical occurrence during the clinical study: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical operations or intervention for preventing from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect. *(Good Clinical Practice for Medical Devices -Article 93)*
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.* *NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.* *(ISO 14155:2011 section 3.1)*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. *(ISO 14155:2011 section 3.36)*
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. *NOTE: Anticipated serious adverse device effect (ASADE) is an effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.* *(ISO 14155:2011 section 3.42)*
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.* *(ISO 14155:2011 section 3.15)*
	Any unreasonable risk caused by a medical device in normal use during clinical study that may endanger human health or life safety, such as label error, quality issues, malfunction and etc. *(Good Clinical Practice for Medical Devices -Article 93)*

Medical occurrences that are inherent to a surgical procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include, but are not limited to, those listed in Table 11-2. These medical occurrences should not be reported as adverse events during this study.

Table 11-2 Expected, non-reportable events related to a surgical procedure

Event Description	Timeframe (hours) from the procedure
Anesthesia related nausea / vomiting (with or without treatment)	24
Low-grade fever (<37.8°C)	48
Pain at access site (with or without standard treatment and patient not returning to clinic to have additional treatment)	72
Mild to moderate bruising / ecchymosis at access site(s) as determined by physician	168
Sleep problems (insomnia) (with or without treatment)	72
Back pain related to laying on table (with or without treatment)	72
Bleeding at access site (not requiring treatment)	24

MACE and Stent Thrombosis

MACE and/or stent thrombosis events should be reported through eCRF immediately after the Investigator and/or other study designated staff becomes aware of the event.

11.2. Evaluation and Documentation of Adverse Events

Investigators are required to evaluate and document all AE (including SAE) and Device Deficiencies (per the definitions in Table 11-1) from the time subjects are consented until they are no longer participating in the study.

For all observed AEs, investigators should assess and document the information on the Adverse Event and/or non-subject AE eCRF.

In addition, for all endpoint events, sites should submit relevant information to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication of the event.

11.3. Anticipated Adverse Events

Latest list of adverse events that are anticipated for subjects participating in this study is described in the Resolute Onyx IB (see appendix 7) and Resolute Integrity IFU (see appendix 6).

11.4. Reporting of Adverse Events

All AE information will be collected in this study. Investigators should provide continuous monitoring, assessment and documentation of the adverse events throughout the duration of the study. Therefore, all AE information will be collected from subjects are consented through the 5-year follow-up assessment.

A list of AEs that may be associated with the use of the study device and/or the interventional procedure is provided in the IB and IFU. AE reporting requirements are provided in Table 11-3. Initial reporting may be done by phone, fax, e-mail, or on the eCRF completing as much information as is available. The original fully completed AE eCRF must be submitted to Medtronic as soon as possible.

In case the investigator requires information from Medtronic in an emergency situation, the investigator may contact Medtronic. A list of contact information will be kept separately.

Adverse event (AE) reporting will be completed according to local regulatory requirements. Note that ISO definitions are used for adverse event classifications. The AE review and reporting process will be specified in this section 11 and/or the clinical safety management and potential complaint plan.

How long to follow an AE (*AEs should be followed until one of these criteria is met***):**

- Until the AE resolves
- Until no further action can be taken for an ongoing AE
- Until the subject exits the study, or
- Until study closure

NOTE: In the case of permanent impairment, continue to follow the event until it stabilizes and the overall clinical outcome has been ascertained

11.5. Documentation and Reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic.

All Device Deficiencies, regardless if it led to an AE, must be reported. Information reported on the Device Deficiency Form shall include a description of the deficiency, the date of onset, actions taken as a result of the deficiency, and the date the deficiency was first noticed by the investigator.

Device deficiencies that did not lead to an adverse event but might have led to an SAE if a) a suitable action had not been taken, or b) an intervention had not been made, or c) circumstances had been less fortunate, should be reported to Medtronic as soon as possible. Initial reporting may be done by phone, fax, e-mail, or on the eCRF completing as much information as is available. The original fully completed Device Deficiency eCRF must be submitted to Medtronic as soon as possible.

Table 11-3 AE Reporting Requirements

For the following events, reporting requirements are: - Serious Adverse Events (SAE)	
Investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical study in clinical Research institutions in written form. Management department of medical device clinical study shall report to:	
Medtronic	Immediately
Local food and drug regulatory authority and health and family planning competent authority of the province, autonomous region and municipality directly under the central government where the clinical Research institution locates	Within 24 hours
Ethics Committee	Within 24 hours/per EC's requirements
For the following events, reporting requirements are: - All other AEs - All other Device Deficiencies	
Investigators shall record all the adverse events and device deficiencies occurred during the clinical study. Investigators shall analyze the reasons for the events with Medtronic and document the analysis result in written report, including the comments of continuing, suspending or terminating study, which shall be reported to the Ethics Committee through management department of medical device clinical study in clinical Research institutions for review.	
To Medtronic	Submit in a timely manner after the investigator first learns of the event.
To Ethics Committee	Per EC's requirements
For the following events, reporting requirements are: • **Serious Adverse Events (SAE)** • **DD with SADE potential**	
Medtronic submits to:	
The food and drug regulatory authorities and health and family planning competent authorities at the same level	Within 5 working days upon being informed
Other clinical Research institutions and investigators participating in the study	As per local reporting requirement

Ethics Committee	Timely report to EC of the clinical Research institution through management department of medical device clinical study

NOTE: In case there is/are additional AE reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific AE reporting requirement and process must be documented in a separate cover.

11.6. Emergency Contact Details

Investigators should contact their Medtronic clinical research specialist or site monitor if they have any questions regarding reportable AE. Medtronic will provide and maintain a listing of current contact details for each site.

12. Data Review Committees

12.1. Clinical Events Committee (CEC)

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of clinical events and clinical endpoints in this study. The CEC is made up 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 Safety Department or designee will categorize all clinical events and provide this information, along with all available source documentation to the CEC. The CEC will meet regularly to review and adjudicate all events in which the required minimum data are available.

Details will be documented in the Charter of the Clinical Events Committee.

13. Statistical Design and Methods

13.1. Statistical Design, Methods and Analytical Procedures

This study is a pre-market, prospective, multi-center, open-label, randomized controlled study aimed to evaluate the clinical safety and efficacy of the Resolute Onyx Stent System, compared with the Resolute Integrity Stent System in subjects that are eligible for percutaneous transluminal coronary angioplasty (PTCA) in *de novo* lesions amenable to treatment with either of the two stent systems in China. The primary endpoint is in-stent Late Lumen Loss (LLL) at 9 months post procedure as measured by Quantitative Coronary Angiography (QCA).

13.1.1. Statistical Analysis Method

Descriptive Analysis：Categorical data will be described using counts and percentages. Continuous data will be described using means, standard deviations, maximum, minimum, medians, the 25th and the 75th percentiles.

Baseline Demographics Analysis: Based on the descriptive analysis, categorical data will be compared between the two groups using Chi-square test with continuity correction, and when more than 25% of the cells of the contingency table have a frequency less than 5, then Fisher's exact test will be used. Continuous variables with normal distribution will be tested using two sample t-test, and non-normal continuous data will be tested with Wilcoxon Rank Sum test.

Effectiveness Analysis: For the primary endpoint, 9 –month LLL, the two arms will be compared using analysis of covariance (ANCOVA) with baseline (post procedure MLD) and sites as covariates. The LLL of the two arms will be provided, and the treatment difference as well as the corresponding 95% confidence interval will be estimated using the least squares estimation. Other effectiveness endpoints will be analyzed using similar method as baseline analysis.

Safety Analysis: Adverse event will be reported with event counts and percentages, and will be compared using chi-square test or Fisher exact test. Meanwhile, the symptom, severity and the relation to investigational devices of all adverse events will be described in a detailed manner.

All statistical analyses will be performed with two-sided 0.05 significant level. Statistical software SAS® 9.4 or higher will be used.

13.2. Sample Size Calculation Consideration

13.2.1. Total Sample Size

According to the CFDA DES clinical study guideline (draft version for public comments), at least 400 evaluable subjects will be 1:1 randomized.

The primary endpoint to be evaluated in this trial is in-stent late lumen loss (LLL) at 9 months post-procedure. In the historical Resolute China RCT trial, the observed in-stent late lumen loss at 9 months was 0.16 ± 0.38 mm for the Resolute arm.[6]

The null hypothesis for this study is that the Resolute Onyx study arm will have a primary endpoint of in-stent late lumen loss at 9 months equal to or exceeding that of the Resolute Integrity control arm by 0.16 mm or more. The alternative hypothesis is that the Resolute Onyx study arm will have 9 months in-stent late lumen loss less than that of the control arm plus 0.16 mm. Rejection of the null hypothesis will signify that the Resolute Onyx stent is non-inferior to the Resolute Integrity stent with regard to 9 months in-stent late lumen loss.

Specifically, the null (H_0) and alternative (H_1) hypotheses are:

H_0: $\mu_A \geq \mu_C + \delta$

H_1: $\mu_A < \mu_C + \delta$

Where μ_A is the true in-stent late lumen loss for the Resolute stent and μ_C is the true in-stent late lumen loss for the control stent.

The parameter assumptions are:

$\mu_A = \mu_C$

Common standard deviation of 0.4 mm

$\delta = 0.16$ mm

Two sided $\alpha = 0.05$

1:1 randomization

25% lost to angiographic follow up

With these assumptions, a total of 534 subjects (400 evaluable, 200 in each group) will yield 98% power to reject the null hypothesis of inferiority in favor of the alternative hypothesis of non-inferiority. To be more conservative, it is planned to enroll approximately 550 subjects.

Power Analysis and Sample Size (PASS) was used to compute sample size.

13.2.2. Minimum and Maximum Enrollment Number per Site and Rationale

This trial will be conducted simultaneously at multiple sites. In principle, every effort will be tried to make the enrollment distributed evenly to each site, to ensure adequate representation of each site. However, in consideration of the feasibility and the enrollment progress, the enrollment will be adjusted according to the real situation, to ensure the enrollment numbers

[6] Xu B, Yang Y, Yuan Z, et al. Zotarolimus-and paclitaxel-eluting stents in an all-comer population in China: the RESOLUTE China randomized controlled trial[J]. JACC: Cardiovascular Interventions, 2013, 6(7): 664-670.

among different sites are relatively balanced. For any specific site, the maximum enrollment number should not exceed 20% of the total sample size.

13.3. Significant Level and Statistical Power

Refer to section 13.2.1 for the level of significance (two-sided 0.05), and the power (98%).

13.4. Expected Drop-out Rate

In this RCT trial, because the subjects need to receive invasive assessment during primary endpoint angiographic follow-up, so based on the historical experience, the expected drop-out rate of this trial is up to 25% (only for the angiographic follow-up).

13.5. Trial Result Pass/Fail Criteria

For Primary Endpoint Analysis

The study pass/fail criteria is based on statistical hypothesis and the final analysis results.

The primary objective of this study is to evaluate the in-stent late lumen loss (LLL) at 9 months, defined as the difference between the post-procedure minimal lumen diameter (MLD) and the follow-up angiography MLD, of the Resolute Onyx Stent System compared to Resolute Integrity Stent System in the de novo population requiring stent implantation in China. If the upper limit of the two sided 95% confidence interval of the difference of the primary endpoint is less than δ, then Resolute Onyx stent is considered non-inferior to Resolute Integrity stent.

13.6. Early Termination of the Trial Based on Statistical Rationales

Interim analysis and corresponding early termination criteria are not planned for this trial. So this section is not applicable.

13.7. Analysis Data Set, Handling of Missing Data, Unused or Erroneous Data (including withdrawals) and Spurious Data

For the possible missing data during the trial, in general missing data will only be imputed for the primary endpoint analysis. The imputation method will be specified in the Statistical Analysis Plan (SAP). However, for this coronary stent trial which uses Late Lumen Loss as the primary endpoint, the expected lost to 9 months angiographic follow up rate can be up to 25%, so missing data imputation may cause bias. So this trial will use all observed available data for primary analysis, and if necessary, will also use multiple or single imputation as secondary analysis or supplementary analysis. For missing data related to other measures, imputation will not be performed. More details will be provided in SAP.

Erroneous or spurious data will be cleaned before performing statistical analysis. The data of withdrawal subjects will also be included in the final statistical analysis. Reasons for withdrawal will be specified in the statistical report. The missing of primary endpoint data caused by early withdrawal will be handled with the methods for missing data as mentioned above.

13.8. Deviation from Pre-specified Analysis Plan

The statistical analysis plan (SAP) will be confirmed by the sponsor and the coordinating investigator/leading site, and finalized before the database is locked for analysis. The SAP may be modified according to the actual scenarios observed during the study phase before final approval. In principle, major analysis principle, methods or analysis sets will not be changed. All revisions will be recorded.

13.9. Criteria and Rationale for Selection of Subjects for Analysis

Statistical analysis sets should be clearly defined prior to the time when analysis is carried out. The analysis sets for this study are defined as follows:

Full Analysis Set (FAS): According to the Intention to treat (ITT) principle, all subjects who have participated in the trial and used the investigational devices, will be included in the FAS.

Per-Protocol (PP): Subjects who finished the trial, excluding those who had major protocol deviations (subjects did not meet all of the inclusion criteria or none of the exclusion criteria).

The primary endpoint analysis will be performed in both FAS set and PP set. Besides, all baseline demographics and secondary efficacy analysis will be performed in FAS set. Safety assessment will also be performed in FAS set (so will not define SS set separately).

14. Ethics

14.1. Statement(s) of Compliance

The study shall be conducted in accordance with the Declaration of Helsinki 2013 and applicable local regulations, Good Clinical Practice for Medical Devices (CFDA Order No.25), CIP, the clinical study agreement, and the ethical principles that have their origin in the Declaration of Helsinki 2013.

The principles of the Declaration of Helsinki have all been implemented by means of the patient informed consent process, EC approval, study training, clinical study registration, preclinical testing, risk benefit assessment, and publication policy. Pediatric, legally incompetent, or other vulnerable subjects are not eligible for the study.

The study will not begin until EC and regulatory authority approvals/notification, as appropriate, are received.

14.2. Role of Medtronic

As the Sponsor of this clinical study, Medtronic has the overall responsibility for the conduct of the study. In this study, Medtronic will have certain direct responsibilities and may delegate other responsibilities to consultants and/or contract research organizations.

The sponsor will avoid improper influence on, or inducement of the subject, monitor, and investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements, EC approval.

No medical care will be provided for subjects after the study has been completed and subject will be treated according to the standard routine practice after the study period. In addition, there is no post-study access of the investigational device for participants as initial treatment and the need for additional devices is not anticipated.

14.3. General Duties

Medtronic's general duties consist of submitting applications and information to appropriate regulatory authorities, obtaining regulatory and EC approvals, selecting qualified Investigators, ensuring proper clinical site monitoring, ensuring subject informed consent is obtained and ensuring that the EC 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, EC and relevant regulatory authorities of safety events and deviations from the investigation plan as appropriate. The Medtronic Clinical Study Team will make sure the written progress reports and a final report were submitted to regulatory authorities and site ECs.

14.4. Ethics Committee (EC)

The study will be conducted in accordance with the requirements of local Ethics Committees. The responsible Ethics Committee (EC) at each investigational site must approve the study

protocol and consent. Study activities will not commence prior to receipt of documentation of EC approval by the site and Medtronic. The Investigator and study site staff must comply with the requirements of their EC.

Prior to enrolling subjects, each investigational site's EC will be required to approve all necessary study documents including the CIP, the Informed Consent Form (ICF) and any other written information to be provided to the subjects. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the study at an investigational site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. If the EC approval letter is not in English, the Medtronic clinical study team must ensure documented review of the letter in English, or a translation to English must be obtained. In addition the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other site study staff, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. Medtronic will prepare the required documents and send them to the investigator for reporting to the EC. Investigators must inform Medtronic of any change in status of EC approval once the investigational site has started enrollment. If any action is taken by an EC with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

14.4.1. General Study Requirements

Prior to enrolling any subjects in the study, all requirements need to be fulfilled. Each site must have written documentation of site/Investigator readiness, including but not limited to EC approval, a signed investigator agreement, and site research personnel training documentation. The Investigators shall agree to this protocol and any amendments by signing and dating the investigator agreement.

The participating Investigator is responsible for adhering to this CIP, the Declaration of Helsinki 2013, the agreement and the applicable local regulatory requirements.

14.4.2. Informed Consent and Ethics Committees

All subjects must provide written informed consent in accordance with approved by the site's EC and Medtronic. A copy of the informed consent form from each site must be forwarded to Medtronic for review and approval prior to submitting it to the EC. 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 EC approval letter and the EC approved informed consent form. Approvals for the continuation of the study at each investigational site must be kept current and notifications forwarded to Medtronic.

15. Regulatory Consideration

15.1. Regulatory Submission

Study documents will be submitted to Regulatory Authority according to CFDA Announcement 2015 No.87, prior to commencement of study. If the regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

Additionally, this study will comply with an administrative permission filing requirement from the Human Genetic Resources Management Office (HGRM). This filing requirement is named as 'Sampling, Collection, Transaction, Export and Outbound Transfer of Human Genetic Resources' administrative permission filing.

During the study, safety information (SAE, etc.) will be submitted to Regulatory Authority according to CFDA Order No. 25 within the required time.

Primary endpoint CSR and subsequent CSRs, along with the CIP, will be submitted to CFDA as part of the product registration application.

16. Study Administration

16.1. Investigator and Investigational Site Selection

Investigators selected will be responsible for fulfilling the clinical study requirements specified in this investigation plan. The investigational site must have the necessary experience and resources to comply with the requirements. The following criteria will be used to select investigators and investigational sites for participation in the clinical study:

- Site should appoint a medical person responsible for clinical study who has related specialty, qualification or title as at least assistant senior in the clinical research institutions, such as associate chief physician, associate professor, or associate researcher or equivalent.
- Investigation sites must be the institutions qualified for conducting clinical study by the regulatory department of CFDA and the Administrative Department of Health under the State Council.
- Investigator is qualified by training and expertise in the diagnosis and treatment of subjects requiring a percutaneous coronary intervention (PCI) procedure with a drug-eluting stent.
- Investigator and clinical research staff have experience with conducting clinical device study that comply with applicable regulatory standards studies and have the time to conduct the study in accordance with the investigation plan.
- Agreement to comply with the investigation plan and applicable regulatory requirements.
- Adequate volume of potential subjects who meet the eligibility criteria
- Number of simultaneous competing clinical studies that might interfere with subject enrollment or study conduct.
- Appropriate facilities, resources, and equipment.
- An expressed desire to participate in the study.
- Willing to undergo monitoring and auditing by Medtronic or relevant regulatory authorities.
- Willing to undergo required study training.
- Willing and able to complete study initiation activities in a timely manner (i.e., within 2 to 3 months)
- Site must have a high-speed Internet connection to ensure an acceptable speed of data transfer.
- All investigational sites and investigators will sign the appropriate Clinical Investigation Agreement before they are accepted for the clinical study.
- Throughout the conduct of the study, Medtronic and/or its designees will closely monitor compliance with the investigation plan, the applicable local laws and regulations, the requirements of the EC, and the terms of the Clinical Study Agreement. Medtronic may suspend or terminate the study prematurely at any site with repeated occurrences of significant non-compliance.

16.1.1. Investigator Responsibility / Performance

The Investigator is responsible to ensure that all work and services related to this study described herein, or incidental to those described herein, are conducted in accordance with the medical practice and Good Clinical Practice for Medical Devices (CFDA Order No. 25), the requirements of the EC, the investigation plan, and the terms of the Clinical Study Agreement and all applicable local laws.

The Investigator will provide copies of the current study Investigation Plan to all authorized Sub-Investigators or other staff members responsible for the conduct of the study.

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

16.1.2. Training of Investigational Sites

Medtronic and/or its designees are responsible for ensuring the training of appropriate clinical site personnel, including the Investigator, Sub-Investigator(s), Research Coordinator(s), and as necessary other site personnel as appropriate (e.g. cath lab personnel). Initial training will be conducted by Medtronic or its designees before study site activation to ensure proper reporting of adverse events, device usage, uniform data collection and compliance with the Investigation Plan (i.e., protocol and consent processes). The site Principal Investigator has to be trained by Medtronic or its designees. Training will consist of, at a minimum, a review of the device IB, IFU, protocol, techniques for the identification of eligible subjects, instructions on data collection, the electronic data capture system, study schedules, and applicable China regulations. Medtronic and/or its designees are responsible for training of key site personnel appropriate to the tasks they have been delegated by the site Principal Investigator. Medtronic and/or its designees and/or the site Principal Investigator can conduct full study training for site personnel who were not trained prior to study site activation. Ongoing assistance regarding completion and submission of eCRFs as well as retraining (if necessary) will be provided by Medtronic and/or its designee.

An individual Training Record must be signed and dated by appropriate person (Medtronic and/or its designee or the site Principal Investigator) conducting the training, and each member of the research team that attended the training session. Site personnel assigned to the study after the initial training visit will undergo full training, which must be documented via submission to Medtronic of a signed Training Record, before any study activity is performed.

Signed training records must be submitted to Medtronic and a copy of each training record retained in the Investigator Site File (ISF).

16.1.3. Clinical Investigation Agreement

A Clinical Investigation Agreement shall be entered into effect by the participating site and/or the principal clinical investigator at each site as per the local legal requirements, and returned to Medtronic prior to the commencement of any study activities. The investigator is indicating approval of the Protocol and subsequent amendments, by signing and dating the agreement. Amendments to this protocol shall be agreed upon between Medtronic and clinical investigator(s) and be recorded with a justification for the amendments.

16.1.4. Curriculum Vitae

Recent signed and dated curriculum vitae from each investigator participating in this study, evidencing the required qualifications, including the year and where obtained, and shall include their current position at the site.

16.2. Monitoring

Monitoring visits and/or remote reviews will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. Investigational sites will be monitored to ensure compliance with the study protocol (including the informed consent process), adherence to applicable regulations, accuracy of study data, and to ensure the safety and wellbeing of the subjects is preserved. Prior to subject enrollment, an initiation visit will be completed with each site. Monitoring visits will also be used to verify that study data submitted on case report forms are complete and accurate with respect to the subject records and to verify device accountability.

Site personnel will complete electronic case report forms (eCRFs) following each subject study schedule. Study data submitted will be reviewed against subject charts and other sources containing original records of subject data.

Upon study completion, Site Closeout Visits will be conducted, as outlined in the Monitoring Plan.

Medtronic will provide monitoring and monitoring oversight. Representatives of Medtronic (i.e. contractors and designees) may also act as the study monitors to the site.

Prior to the first site activation a monitoring plan will be established outlining the activities, as well as study materials to be supplied to sites, the process for corrective and preventive actions and Investigator disqualification procedures. 100% of source data verification (SDV) will be performed and extent of SDV will be described in the monitoring plan.

The principal investigator(s), his/her delegate(s) and the study coordinator(s) are expected to be present and available during the monitoring visit to discuss monitoring outcomes. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

16.3. Audits and Inspections

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to assess clinical study activities independently of the personnel directly involved in the study. Regulatory authorities and ECs may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and Regulatory Authority direct access to source data and documents. Any Regulatory Authority inspection announcements shall be forwarded immediately to the Medtronic Clinical Study Manager of this study. A list of contact information will be kept separately.

16.4. Data Management

Medtronic will oversee all data management functions and provide support if necessary. Leading site will be accountable for data management and analysis about the study data in a centralized manner according to local regulations.

16.4.1. Case Report Forms

Study sites will assign a unique study ID number to each subject, as applicable. Records of the subject/ID relationship(s) will be maintained by the study site. Individual subject medical information obtained as a result of this study will be considered confidential.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the subject medical file.

Only authorized persons can complete CRFs. CRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in eCRFs. If a person is only authorized to complete eCRFs or to make changes to an already signed eCRF, the investigator shall re-sign this eCRF. All required data for this study will be collected on standardized electronic Case Report Forms (eCRFs).

16.4.2. 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 investigation 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
2. Description of device implantation procedure (material used, drugs administered during the procedure, date, time, angiographic and clinical findings, etc.)
3. Dated and signed notes for each study subject visit including results of examinations
4. Notations on abnormal lab results and their clinical significance/resolution
5. Dated printouts or reports of special assessments, (e.g., ECG reports, blood tests)

6. 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)
7. Notes regarding concomitant medications taken during the study (including start and stop dates)
8. Study subject's condition upon completion of or withdrawal from the study

Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigation site team indicating they are a true reproduction of the original source document.

The eCRFs will not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from site to site: the site may use worksheets if identified as source documents.

16.4.3. Transmission of Data

Required data will be recorded on the appropriate electronic Case Report Forms 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.

16.4.4. Data Queries

During the review of source documents and eCRF at the monitoring visits, any discrepancies will be queried by Medtronic or its designee and must be resolved by the investigational site staff and investigator in a timely manner.

16.4.5. Time Windows for Completing Case Report Forms and Reports

Table 16-1 Investigator Reporting Guidance for Submitting Data

Type of CRF/Report/Data	Expected Completion by Site within	Process
Investigational device usage	2 business days or as soon as available	Submit within 2 business days
CRFs (e.g., Inclusion/ Exclusion, Baseline, Report of Noncompliance, Study Exit Form)	10 business days or as soon as source documents available	Submit via EDC
Angiograms (Baseline and clinical events)	10 business days or as soon as available	Site to send media to Core Laboratory within 10 business days of data collection

16.4.6. Electronic Clinical Data Systems

Data will be captured in an electronic data capture system.

16.5. Study Materials and Study Specific Equipment

Medtronic will control the supply of investigational devices and study materials (e.g. Investigator Site File, eCRF access). Investigational devices will not be sent to the site until the site is activated. Medtronic will not provide any study-specific equipment to the sites.

16.6. Device Accountability

In this study, both Resolute Onyx Stent System and Resolute Integrity Stent System are considered as study devices. As such, they should be stored in a secure location. The method of storage should prevent the use of these investigational devices for other applications than mentioned in this CIP. Sites are required to maintain investigational device records that contain the following information:

- Investigational device name
- Serial number / Lot number
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device
- Date of implant or use
- ID number of subjects receiving or using the device
- Disposition (implanted, disposed of, or returned to Medtronic)

For devices that are returned to Medtronic or disposed of, sites are required to document the following information:

- The device serial numbers / Lot numbers
- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic

Device accountability records must be maintained at the study site. The quantity of devices received by the study site, those returned, and those devices used at the study site will be recorded in device accountability records. The Investigator or an authorized designee must explain in writing the reasons for any discrepancy noted in device accountability. When the study enrollment is complete, the Investigator shall return any unused devices, opened or unopened, to Medtronic.

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.

Note: for additional information on shipment, receipt, and return of study devices refer to the device tracking instructions.

16.7. 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 [e.g. site number, subject number and randomization 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.

16.8. CIP Amendments

As appropriate, Medtronic will submit changes in the clinical investigation plan to the appropriate regulatory authorities and to Investigators to obtain EC re-approval as required. Furthermore investigators shall sign any approved amendment.

16.9. Record Retention

Records must be maintained by the investigator in compliance with national regulations. Investigator records including the Investigator Site File, subject medical files and CRFs are subject to regulatory inspection (and Medtronic) and copying, and must be retained for a period of 10 years after the investigation is completed or terminated, 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, EC, Medtronic, a monitor, or regulatory agencies, 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 case report forms 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 investigation 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 Clinical Research Department should be contacted if the Principal 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 until no Resolute Onyx and Resolute Integrity are used, or at least 15 years, whichever is longer.

16.10. Publication and Use of Information

Publications based on the results of the study will follow the process outlined in the Clinical Study 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 approval of Medtronic.

Additional secondary manuscripts with principal authorship drawn from members of this study's investigators 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 Investigators 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.

16.11. Suspension or Early Termination

Medtronic, Investigator, EC 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 investigation 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.
- Interim analysis indicates that the results significantly differ from the clinical study objectives or statistical endpoints

In case of study suspension and termination, the investigator shall timely notify the subjects and assure they will obtain with proper treatment and follow-ups.

If decision is made to suspend or terminate a clinical study, within 5 days, Medtronic shall notify, with a written explanation, all the management departments of medical device clinical study in the clinical research institutions, which will in turn notify investigator and EC. The suspended clinical study must not be recommenced without the approval from EC. After the clinical study closure, Medtronic shall notify in written its local Food and Drug Administration (province, autonomous region or municipality as appropriate) where it locates.

Investigator must inform the subjects, Medtronic, the Ethic Committees and relevant regulatory authorities respectively of such a discontinuity case with rationale if the decision of suspension or early termination of the study is made by the investigator.

Medtronic shall ensure that all investigators who conduct the clinical study comply with the clinical investigation plan. In case a clinical research institution and an investigator are found failed to comply with relevant laws and regulations, Good Clinical Practice for Medical Devices (CFDA Order No. 25) and this clinical investigation plan, Medtronic shall identify it and implement a course of corrective actions. For serious case or continued case without rectification, Medtronic should terminate the study at this clinical research institution and notify the local Food and Drug Administration (province, autonomous region or municipality as appropriate) where this clinical research institution locates and CFDA.

16.12. Study Close-Out

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up assessments and the CRFs and queries have been completed), Medtronic and/or its designees will notify the site of closeout and that notification to EC and regulatory authority will be done, if required. A study closeout visit may be performed if defined in the monitoring plan. 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.

16.13. Clinical Study Registration

The registration process in a public registry clinicaltrials.gov will be followed.

16.14. Investigator Reports

The investigator is responsible for the preparation and submission of the reports cited in the Table 16-2. 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 EC may request reports pertaining to any aspect of the clinical study.

Table 16-2 Investigator Reporting Responsibilities

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of EC Approval	Medtronic	The investigator must report a withdrawal of the reviewing EC's approval of the investigator's part of the investigation within 5 working days.

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Progress Report	Medtronic, EC	The investigator must submit this report at least annually or more often if required by EC for the duration of the study. Copy of submitted report to be provided to Medtronic
Deviation from Investigation Plan (Emergency)	Medtronic & EC	Notification must be made as soon as possible if the deviation was made to protect the life or physical wellbeing of a subject.
Deviation from Investigation Plan (Other – Non Emergent)	Medtronic & EC	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 9.10 Deviation Handling).
Failure to Obtain Informed Consent	Medtronic & EC	The Investigator must notify Medtronic and the reviewing EC within 5 business days after device use. The report must include a brief description of the circumstances justifying the failure to obtain informed consent.
Final Report	Medtronic, Regulatory Authorities & EC	This report must be submitted within 3 months after termination or completion of the investigation. Copy of EC submitted report to be provided to Medtronic.

NOTE:

1. The investigator will report to the EC and Medtronic in a timely manner through the management department of medical device clinical study in clinical research institution.

2. In case there is/are additional reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific reporting requirement and process must be documented in a separate cover.

17. Insurance

If subjects are physically injured as a result of participation in this study, reasonable and appropriate medical treatment will be provided by Medtronic, if such treatment is not already covered by subject's medical insurance according to the local requirements. The local sponsor Medtronic (Shanghai) Management Co, Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable laws and customs concerning specific insurance coverage. If required, a Clinical Study Insurance statement/certificate will be provided to the EC.

18. Study Reimbursement

Funding for the study will be defined according to the local regulations and must be agreed upon in writing by the clinical research institution and Medtronic before the study commences. The payments for the study should be appropriate relative to the number of subjects enrolled. The Resolute Onyx™ Stent System and Resolute Integrity™ Stent System will be provided by Medtronic free of charge for use in this clinical study. A reasonable amount of the angiography procedure and travel expense for the 9-month angiographic follow-up will be reimbursed. No any other compensation for the participation in this study will be provided by Medtronic.

19. Reference

The related references have been inserted in the footnote where applicable.

20. Appendixes

Appendix 1 Study Contacts

Sponsor:	Medtronic, Inc. 710 Medtronic Parkway Minneapolis, MN 55432, USA
Local Sponsor (Project & Site Management):	Medtronic (Shanghai) Management Co., Ltd Room 2106A, 2106F, 2106G, 2106H, Floor 21, Donghua Financial Building, No. 28 Maji Road, China (Shanghai) Pilot Free Trade Zone, 200120, Shanghai, P.R. China
Clinical Operations:	Medtronic, Inc. Medtronic Core Clinical Solutions Strategy and Scientific Operations 710 Medtronic Parkway, LS330 Minneapolis, MN 55432
Monitoring & Site Management	R&G Pharma Studies Co., Ltd. Floor11, North Tower, Building B, Huatong Plaza, No.19 Chegongzhuangxilu, Haidian District Beijing, 100048, China Phone : (86) -10-88018650 Fax : (86) -10-88019978 Website : www.rg-pharma.com
Clinical Events Committee:	Cardiovascular Research Foundation 111 East 59th Street, 12th Floor New York, NY 10022 Phone : (646) 434-4122 Fax : (646) 434-4508 Website : http://www.crf.org
Angiographic Core Lab:	Cardiovascular Research Foundation 111 East 59th Street, 12th Floor New York, NY 10022 Phone : (646) 434-4122 Fax : (646) 434-4508 Website : http://www.crf.org

The detailed contact list will be kept separate from the CIP and provided to the investigators. Medtronic will maintain an updated list. For specific contact information of the core members (e.g. Medical expert) refer to the detailed list.
For the relevant qualification documents of Medtronic refer to the EC review document package.

Appendix 2 List of Definitions

ACUTE CLOSURE

Acute Closure: 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.

Sub-acute Closure: Abrupt closure that occurred after the procedure is completed (and the left the catheterization laboratory) and before the 30-day follow-up evaluation.

Threatened Acute Closure: A grade B dissection and ≥ 50% diameter stenosis or any dissection of grade C or higher.

ACUTE GAIN

The immediate dimensional change in minimal luminal diameter (mm) that occurred after the final post-dilatation as compared to the minimal luminal diameter at baseline and measured by quantitative coronary angiography from the average of 2 orthogonal views.

ACUTE SUCCESS

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

Device Success:

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

Current definition: The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) **AND** a TIMI flow 3 after the procedure, using the assigned 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: The 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 a 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: The 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 a 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.

ANGIOGRAPHIC BINARY RESTENOSIS (ABR) RATE

Percent of subjects with a follow-up percent diameter stenosis of ≥ 50%.

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

A ≥ 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.

BLEEDING COMPLICATION

A procedure related hemorrhagic event that requires a transfusion or surgical repair. These may include a hematoma requiring treatment of retroperitoneal bleed.

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

Severity:

Class 1: New onset of severe or accelerated angina. Patients with new onset (<2 months in duration) exertional angina pectoris that is severe or frequent (>3 episodes/day) or patients with chronic stable angina who develop accelerated

angina (that is angina distinctly more frequent, severe, longer in duration or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding months.

Class 2: Angina at rest, sub-acute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Class 3: Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Clinical circumstances in which unstable angina occurs:

Class A: Secondary unstable angina. Patients in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia. Such conditions reduce myocardial oxygen supply or increase myocardial oxygen demand and include anemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrhythmia, unusual emotional stress, thyrotoxicosis and hypoxemia secondary to respiratory failure.

Class B: Primary unstable angina. Patients who develop unstable angina pectoris in the absence of an extra-cardiac condition that have intensified ischemia, as in Class A.

Class C: Post-infarction unstable angina. Patient who develop unstable angina within the first two weeks after a documented acute myocardial infarction.

CALCIFICATION

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[7,8]

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.

7 Campeau, L.. 2002. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol* 18 (4): 371-9.

8 Campeau L. Letter: Grading of angina pectoris. *Circulation* 54 (3): 522-3.

	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)

The occurrence of cerebral infarction (ischemic stroke) or intracerebral hemorrhage or subarachnoid hemorrhage (hemorrhagic 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**

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 patients 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.

DELIVERY SUCCESS: Complete passage of the stent across the target lesion with full expansion of the stent to the desired diameter at the desired location.

Note: Failed delivery: failure to pass the stent through the guiding catheter into the coronary artery, failure to pass it completely across the target lesion, or failure to expand the stent to its desired diameter. Failed delivery includes proximal deployment defined as those instances of failed delivery when the stent could be advanced only partially across the target lesion but was deployed nonetheless by full expansion.

DEVICE RELATED ADVERSE EVENT

Any adverse event for which a causal relationship between the device and the event is at least a reasonable possibility (i.e., the relationship cannot be excluded).

DIABETES MELLITUS[9]

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)10, 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 study a patient 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. Patients who are taking insulin, or both insulin and oral agents, will be classified as insulin dependent. Patients who are taking oral agents only, a modified

9 Report of the expert committee on the diagnosis and classification of diabetes mellitus. 2003. Diabetes Care 26 Suppl 1S5-20.
10 Diabetes mellitus. Report of a WHO Study Group. 1985. World Health Organ Tech Rep Ser 7271-113.

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**[11]

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.

DISTAL EMBOLIZATION

A new abrupt cut off or filling defect distal to the treated lesion.

EMERGENT BYPASS SURGERY

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

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.

IN-SEGMENT MEASUREMENT

The measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.

IN-STENT MEASUREMENT

The measurements within the boundaries of the stent.

11 Detre, K., R. Holubkov, S. Kelsey, M. Bourassa, D. Williams, D. Holmes, Jr., G. Dorros, D. Faxon, R. Myler, K. Kent, et al. 1989. One-year follow-up results of the 1985-1986 National Heart, Lung, and Blood Institute's Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 80 (3): 421-8.

LATE INCOMPLETE APPOSITION

Incomplete apposition of the stent at follow-up that was not present post-procedure. See also incomplete apposition.

LATE LOSS INDEX

The ratio of late loss to acute gain.

LATE LUMEN/LUMINAL LOSS (LLL)

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)[12]

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**.**

MAJOR ADVERSE CARDIAC EVENTS (MACE)

The composite of death, myocardial infarction (Q wave and non-Q wave), 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

12 Smith, S. C., Jr., J. T. Dove, A. K. Jacobs, J. W. Kennedy, D. Kereiakes, M. J. Kern, R. E. Kuntz, J. J. Popma, H. V. Schaff, D. O. Williams, et al. 2001. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 37 (8): 2215-39.

angiography by the Investigator; it is measured during QCA by the Angiographic Core Laboratory.

MYOCARDIAL INFARCTION (MI)

Medtronic extended historical definitions of MI will be utilized for regulatory reporting.

Medtronic Historical Definition of 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 CK-MB 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 CK-MB > 1*URL ***or*** ▪ in the absence of CK-MB: Troponin > 1*URL ***or*** ▪ in the absence of CK-MB and Troponin: CK > 1*URL ***or*** ▪ in the absence of CK-MB 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 : ▪ CK-MB > 1*URL ***or*** ▪ in the absence of CK-MB:, Troponin > 1*URL ***or*** ▪ in the absence of CK-MB and Troponin: CEC decision upon clinical scenario
OR b2. In the absence of CK: CK-MB > 3*URL
OR

b3. In the absence of CK and CK-MB: 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 CK-MB > 1*URL *or* acute MI in progress

MYOCARDIAL INFARCTION, RE-INFARCTION (EXTENSION) <48 HOURS POST PCI
A. If CK (or CK-MB) 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 CK-MB or Troponin > 1*URL) and ≥ 50% above the previous level ***or*** o In absence of CK: a (post PCI) rise in CK-MB within 24 hours of the index event >3*URL and ≥ 50% above the previous level. ***Or*** o In absence of CK and CK-MB: 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 CK-MB) following the index MI has peaked ***AND*** CK level has returned < URL then any new rise in: ▪ CK >2*URL(confirmed by either CK-MB > URL or Troponin >URL) ***or*** ▪ in the absence of CK: CK-MB > 3*URL ***or*** ▪ in the absence of CK and CK-MB, Troponin > 3*URL C. If CK (or CK-MB) 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 CK-MB > URL or Troponin > URL. ***or*** ▪ In absence of CK, when CK-MB has NOT returned < URL, a rise in CK-MB ≥50% above the previous level and > 3 URL. ***or*** ▪ In absence of CK, when CK-MB 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 CK-MB > 1*URL. ***Or*** ▪ in the absence of CK-MB: Troponin > 1*URL ***or*** ▪ in the absence of CK-MB and Troponin: CK > 1*URL ***or*** ▪ in the absence of CK-MB and Troponin and CK: CEC decision upon clinical scenario
B. Appropriate cardiac enzyme data (respecting top-down hierarchy): b1. CK ≥ 2* URL Confirmed by: ▪ CK-MB > 1*URL ***or*** ▪ in the absence of CK-MB: Troponin > 1*URL ***or*** ▪ in the absence of CK-MB and Troponin: CEC decision upon clinical scenario ***OR*** b2. In the absence of CK: CK-MB > 3*URL
OR b3. In the absence of CK and CK-MB: 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 CK-MB 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 CK-MB: Troponin > 5*URL ***or*** ▪ in the absence of CK-MB and Troponin: CK > 5 URL ***or*** ▪ in the absence of CK-MB and Troponin and CK: CEC decision upon clinical scenario
B. Appropriate cardiac enzyme data - CK-MB ≥ 10* URL ***or*** - In the absence of CK-MB: Trop > 10*URL. ***or*** - In the absence of CK-MB and Troponin: CK > 10*URL

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

MYOCARDIAL INFARCTION, RE-INFARCTION (EXTENSION) <72 HOURS POST CABG
A. If Peak CK (or CK-MB) 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 CK-MB within 24 hours of the index event >10*URL and ≥ 50% above the previous level. o In absence of CK-MB: a rise in Troponin within 24 hours of the index event >10*URL and ≥ 50% above the previous level. o In absence of CK-MB 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 CK-MB) following the index MI has peaked ***AND*** CK-MB level has returned < URL, any new rise in: ▪ CK-MB >10*URL ***or*** ▪ in the absence of CK-MB: Troponin > 10*URL ***or*** ▪ in the absence of CK-MB and Troponin: CK > 10*URL C. If elevated CK (or CK-MB) following the index MI has peaked ***AND*** CK-MB level has NOT returned < URL: ▪ A rise in CK-MB ≥50% above the previous level and > 10 URL ***or*** ▪ In absence of CK-MB: a rise in Troponin ≥50% above the previous level and > 10* URL. ***or*** ▪ In absence of CK-MB and Troponin: a rise in CK ≥ 50% above the previous level and >10*URL

NO REFLOW

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.

PERCENT VOLUME OBSTRUCTION

Stent intimal hyperplasia and calculated as 100 x (Stent Volume (SV) – Lumen Volume (LV))/SV.

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.

PERCUTANEOUS CORONARY INTERVENTION (PCI)

Refers to all interventional cardiology methods for treatment of coronary artery disease.

PERSISTING DISSECTION

Dissection at follow-up that was present post-procedure. See also "dissection".

PERSISTING INCOMPLETE APPOSITION

Incomplete apposition at follow-up that was present post-procedure. See also "incomplete apposition."

RESTENOTIC LESION

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

REFERENCE VESSEL DIAMETER (RVD)

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

STENT THROMBOSIS

All stent thrombosis data will be reported according the Academic Research Consortium (ARC) definitions[14].

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 patient has left the catheterization lab.

Timing:

Acute stent thrombosis *	0 – 24 hours post stent implantation

[14] Cutlip, D. E., et al. (2007). "Clinical end points in coronary stent trials: a case for standardized definitions." Circulation 115(17): 2344-2351.

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

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:

   a. 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

   b. 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 study follow-up.

STROKE

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

An event where the Investigator or site personnel did not conduct the study according to the investigation plan, applicable laws or regulations, or the Investigator Agreement.

TARGET LESION

Any lesion treated or attempted to be treated during the study procedure with the study device. 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)

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, LCx, 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 (MI)

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[13]

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)[14]

Non-occlusive thrombus: 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 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 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.

13 The Thrombolysis in Myocardial Infarction (TIMI) study. Phase I findings. TIMI Study Group. 1985. *N Engl J Med* 312 (14): 932-6.

14 Capone, G., N. M. Wolf, B. Meyer, and S. G. Meister. 1985. Frequency of intracoronary filling defects by angiography in angina pectoris at rest. *Am J Cardiol* 56 (7): 403-6.

UNSTABLE ANGINA

Per the ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction there are three (3) principal presentations of unstable angina (UA) [15]:

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).

VASCULAR COMPLICATIONS

Vascular complications may include the following:

1. Pseudoaneurysm
2. Arteriovenous fistula (AVF)
3. Peripheral ischemia/nerve injury
4. Vascular event requiring transfusion or surgical repair

15 Braunwald, E., E. M. Antman, J. W. Beasley, R. M. Califf, M. D. Cheitlin, J. S. Hochman, R. H. Jones, D. Kereiakes, J. Kupersmith, T. N. Levin, et al. 2002. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 40 (7): 1366-74.

Appendix 3 Angiographic Core Lab Procedures

Note: A copy of the angiographic core laboratory procedure will be provided in the Investigator Site File, the study binder to the Investigator.

Appendix 4 Sample Informed Consent Form

NOTE: Refer to the most current version of the Sample Patient Informed Consent Form 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 Instructions for Use (Resolute Integrity)

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

Appendix 7 Resolute Onyx stent Investigator's Brochure (IB)

NOTE: Refer to the most current version of the investigator's brochure sent under separate cover.

Appendix 8 Device Label

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

Appendix 9 Investigators and Institutions List

NOTE: Refer to the most current version of the investigator and institution list sent under separate cover.

21. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial release	Dong Li / CSM
2.0	– Statistical Design and Methods: ITT is replaced by FAS. – Table of expected, non-reportable events related to a surgical procedure is added. – Appendix 2 List of Definitions: updated MACE definition	Kevin Lei / CSM