Clinical Study Document Approval Form	
Study Name/Identifier	**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
Document Name	Statistical Analysis Plan (SAP)
Document Version and Date	3.0, 14-Oct-2020
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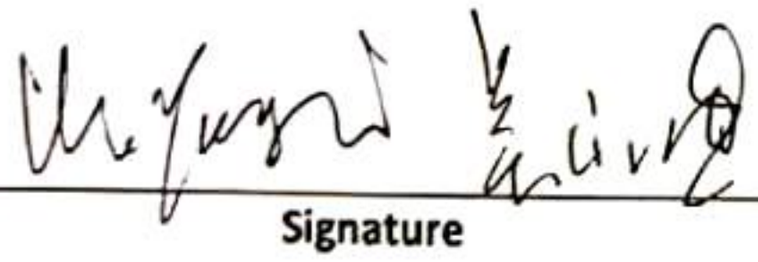
Approver Name: Wu, Yongjian 吴永健	**Role or Title:** Leading Principal Investigator 牵头主要研究者
	04-Nov-2020
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Signed By	Meaning of Signature	Date/Time (UTC)
Zheng, Peter	Clinical Study Manager (CSM)	10/25/2020 07:35:09
Pilcher, Garrett	Biostatistician	10/25/2020 12:16:20
Liu, Minglei, PhD.	Biostatistician	10/25/2020 19:06:08
Lu, Brett	Statistics Programmer	10/26/2020 00:00:11

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Zheng, Peter	Clinical Study Manager (CSM)	10/23/2020 00:30:57
Lu, Brett	Statistics Programmer	10/23/2020 00:32:22
Shen, Cheryl	Biostatistician	10/23/2020 00:58:40

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Statistical Analysis Plan (SAP)

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
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Approvals

The undersigned have reviewed China RESOLUTE Onyx China RCT Study Statistical Analysis Plan (SAP) and agree with its contents.

e-signature

Pilcher, Garrett,	**Senior Clinical Research Director**	**Date**

e-signature

Liu, Minglei,	**Senior Statistics Manager**	**Date**

e-signature

Zheng, Peter,	**Clinical Study Manager**	**Date**

e-signature

Lu, Brett,	**Statistical Programmer**	**Date**

Clinical Study Document Approval Form	
Study Name/Identifier	**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
Document Name	Statistical Analysis Plan (SAP)
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Approver Name: Wang, Yang 王杨	**Role or Title:** Director of Medical Statistics Department NCCD, NCCD 医学统计部总监
Yang Wang 王杨	22-OCT-2020
Signature	**Signature Date (DD-MMM-YYYY)**

Approver Name: Zhao, Yanyan 赵延延	**Role or Title:** Biostatistician NCCD, NCCD 生物统计师
Yanyan Zhao 赵延延	22-OCT-2020
Signature	**Signature Date (DD-MMM-YYYY)**

TABLE OF CONTENTS

1. VERSION HISTORY

Version	Summary of Changes	Author(s)/Title
1.0	• Initial release	Yun Peng, Senior Biostatistician
2.0	• Cover page: Changed address of Medtronic (Shanghai) Management Co., Ltd; • ITT was changed as FAS • Sections 7.1, 7.2, 7.5, 7.9: Updated based on discussions between Medtronic statisticians and NCCD statisticians; • Section 7.11: Added more subgroup analysis based on Leading PI suggestions; • Appendix II: Changed the 360-day/year to 365-day/year for visit time windows calculation.	Cheryl Shen, Medtronic Biostatistician Zhao Yanyan, NCCD Biostatistician
2.1	• Approvals page: updated according to 056-F287: Corporate Clinical Approval Matrix • Section 2: added Acronym/Abbreviation related to Resolute Onyx China RCT study; • Section 5.2.1, 7.3, 7.5: Updated • Section Interim analysis was removed (no interim analysis required in this study. i.e. no need to keep the section in SAP) • Section 7.10: Removed Simple and Complex subgroups • CIP version number and date added in cover pager, footer and the date of the document updated	Cheryl Shen, Medtronic Biostatistician
3.0	• Approvals page: updated names of approvers • Section 7.2: specified the out of window stated in PP set is 12M while it is 9M out of window in QCA PP set • Section 7.5: updated the imputation model; corrected typos • Section 7.9: remove tests for adverse events • Section 7.10: add Non-Diabetes subgroup • Appendix: added Appendix III: Subject follow-up window	Cheryl Shen, Medtronic Biostatistician

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronym/Abbreviation	Term
%DS	Percent diameter stenosis
AE	Adverse event
ARC	Academic Research Consortium
CABG	Coronary artery bypass graft
CCSC	Canadian Cardiovascular Society Classification
CRF	Case report form
CSR	Clinical Study Report
cTn	preferably cardiac troponin
CTO	Chronic Total Occlusion

Acronym/Abbreviation	Term
DES	Drug eluting stent
DS	Diameter stenosis
EC	Ethics Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
GI	Gastrointestinal
IB	Investigator Brochure
ISR	In-stent restenosis
ITT	Intent-to-treat
LBBB	left bundle branch block
LIMA	Left internal mammary artery
LM	Left Main
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
mg	Milligram
MI	Myocardial infarction
MLD	Minimum luminal/lumen diameter
µg	Microgram
mm	Millimeter
NMPA	National Medical Products Administration
PCI	Percutaneous coronary intervention
PG	Performance goal
PI	Principal investigator
PP	Per protocol set
PTCA	Percutaneous transluminal coronary angioplasty
QWMI	Q wave myocardial infarction
RCT	Randomized Controlled Trial
RIMA	Right internal mammary artery
RVD	Reference vessel diameter
SAP	Statistical Analysis Plan
SD	Standard deviation
ST–T	ST-segment–T wave
STEMI	ST-elevation myocardial infarction
SVG	Saphenous vein graft
TIA	Transient ischemic attack

Acronym/Abbreviation	Term
TIMI	Thrombolysis in myocardial infarction
TLF	Target lesion failure
TLR	Target lesion revascularization
™	Trademark
TVF	Target vessel failure
TVMI	Target vessel myocardial infarction
TVR	Target vessel revascularization
URL	Upper reference limit

3. INTRODUCTION

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of China 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. The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, the plan has the following purpose: To prospectively outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

4. STUDY PURPOSE

This pre-market study is initiated for Resolute Onyx NMPA 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. The primary objective is 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. INVESTIGATION PLAN

5.1. STUDY DESIGN

The Medtronic RESOLUTE ONYX China RCT Study is a pre-market, prospective, multi-center, open-label, randomized controlled trial 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. This study is designed to assess the non-inferiority of Resolute Onyx stent compared to Resolute Integrity stent in in-stent late lumen loss at 9 months.

5.2. TREATMENT(S) AND SUBJECT ENROLLMENT

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 at a 1:1 ratio. 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.

5.2.1. RANDOMIZATION

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:

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

OR

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

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 should be only treated with assigned Resolute Onyx or 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. Since knowledge of the randomization procedure may lead to selection bias, the randomization procedure therefore will be described in a separate document.

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.

5.2.2. INCLUSION CRITERIA

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

5.2.2.1. 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

5.2.2.2. 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 1 Resolute Onyx™ Stent Size Matrix or Table 2 Resolute Integrity™ Stent Size Matrix

Table 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 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

5.2.3. EXCLUSION CRITERIA

5.2.3.1. 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 3 in Section 5.2.4 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

5.2.3.2. 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

5.2.4. CRITERIA FOR ADDITIONAL PROCEDURES

Table 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		

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

5.3. ENDPOINTS

5.3.1. PRIMARY ENDPOINT

The primary endpoint for this study is Late lumen loss (LLL, in-stent) at 9 months post-procedure as measured by quantitative coronary angiography (QCA).
Note: Per protocol, target lesion is defined as: 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.

5.3.2. SECONDARY ENDPOINTS

Secondary endpoints of this study include the following:
Clinical Endpoints:

- Acute success (device, lesion and 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), 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 Legion 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 (as determined by ARC definitions).

Angiographic Endpoints (at 9 months post procedure):

- In-stent and in-segment percent diameter stenosis (%DS)
- In-stent and in-segment binary 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. DETERMINATION OF SAMPLE SIZE

According to the NMPA 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.[1]

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 sin-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.

[1] 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.

7. STATISTICAL METHODS OF ANALYSES

7.1. ANALYSIS POPULATIONS

(1) Analysis population for clinical follow-up at 12 months post-procedure.

Full Analysis Set (FAS): According to the Intention to Treat (ITT) principle, all subjects who were randomized and used or tried to use the investigational devices (including study device, control device or non-study device) in the trial, will be included in the FAS.
Per-Protocol Set (PP): The subgroup of treatment population that completed the study and had no major protocol deviations (Such as subjects who violated the inclusion criteria / exclusion criteria, did not obtain 12-month TLF, used non-study devices, etc.).

(2) Analysis population for in-stent late lumen loss (LLL) at 9 months post-procedure.

QCA Full Analysis Set (QCA FAS): According to the Intention to Treat (ITT) principle, all subjects who were randomized and used or tried to use the investigational devices (including study device, control device or non-study device) in the trial and derived in-stent late lumen loss (LLL) at 9 months post-procedure, will be included in the QCA-FAS.
QCA Per-Protocol Set (QCA PP): The subgroup of population in QCA-FAS and had no major protocol deviations (Such as subjects who violated the inclusion criteria / exclusion criteria, used non-study devices, etc.).
The analysis of primary endpoint will be based on both QCA FAS and QCA PP. All baseline demographic data analysis will be based on FAS. The secondary clinical endpoints analysis will be based on both FAS and PP. The secondary angiographic endpoints will be based on QCA FAS. The other safety evaluation will be also based on FAS. The safety analysis set (SS) uses the same definition method as FAS, so the SS will be no longer defined separately in the analysis.

7.2. DETAILS OF ANALYSIS POPULATION DETERMINATION AND FLOW CHART

(1) Not obtain any study relevant treatment: Subjects obtained randomization number, but did not receive any study relevant treatment ultimately (including study device, control device or non-study device).
(2) Violate inclusion and exclusion criteria: Subjects do not meet the inclusion criteria set in the protocol or meet the exclusion criteria set in the protocol, and this protocol deviation may severely affect the results of primary effectiveness endpoint. Whether protocol deviation severely affect the results of primary effective endpoints will be judged together by sponsor, investigators and statistician by discussion at blind review meeting.
(3) Not obtain 12-month TLF: Subjects were lost to follow-up at 12 months post procedure and did not occur TLF (defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically driven target lesion revascularization (TLR) by percutaneous or surgical methods, at 12 months) during the 12-month follow-up period.
(4) Not obtain 9-month in-stent LLL: Subjects did not obtain 9-month in-stent LLL. i.e. the subjects did not obtain in-stent LLL during the whole angiographic follow-up period. The subjects who underwent angiographic test and could obtain in-stent LLL prior to 9-month or later than 9-month will be included in QCA FAS for analysis.
(5) Out of time window:
    1) The difference between the 12-month follow-up date after procedure and procedure date of subjects is not in the range of [335,395] days.
    2) The difference between the 9-month angiographic follow-up date after procedure and procedure date of subjects is not in the range of [240,300] days.

    The above two items may severely affect the results of primary effectiveness endpoint. Whether protocol deviation severely affects the results of primary effectiveness endpoint will

be judged together by sponsor, investigators and statistician by discussion at blind review meeting.

(6) Oversize of study devices: The size of the study devices used for subject is not in the range of sizes specified in the study protocol.

(7) Use non-study devices: The devices used for subject are not the study devices specified in the study protocol.

(8) Cross-over: The subjects were randomly assigned to the test group, but received control device actually; or subjects were randomly assigned to the control group, but received test devices actually.

(9) FAS= Number of the ITT subjects – Number of patients who did not obtain any study relevant treatment;

PP= FAS - Number of subjects who had major protocol deviations;

Number of subjects who had major protocol deviations = Number of subjects who violate inclusion and exclusion criteria + Not obtain 12-month TLF + 12M Out of time window + Oversize of study devices +Use non-study devices+ Cross-over;

QCA FAS= FAS - Number of subjects who did not obtain 9-month in-stent LLL;

QCA PP= QCA FAS - Number of subjects who had major protocol deviations;

Number of subjects who had major protocol deviations = Number of subjects who violate inclusion and exclusion criteria + 9M Out of time window + Oversize of study devices +Use non-study devices+ Cross-over;

Priority level of had major protocol deviations: Not obtain 12-month TLF/Not obtain 9-month LLL, Cross-over, Use Non-study devices, Violate inclusion and exclusion criteria, Oversize of study devices, Out of time window. If subjects had two or more above major protocol deviations, they will be classified in accordance with the priority level of protocol deviation.

The major protocol deviations of subjects will be listed based on actual cases after blind review meeting determination. (For example, if the number of subjects who are out of time window is 0, this item will not be displayed in the table). Additionally, the subjects who did not obtain any study relevant treatment or had major protocol deviations will be listed, including the center number, randomization number, group gender, age, deviation type, deviation reason, FAS, PP, QCA FAS and QCA PP.

The above part is the protocol deviation items checked according to the statistical analysis principle by SAS programming. The protocol deviations collected by CRF will also be listed and reviewed by Medical Monitor and PIs for determination of major or minor protocol deviation through blind data review meeting (if applicable).

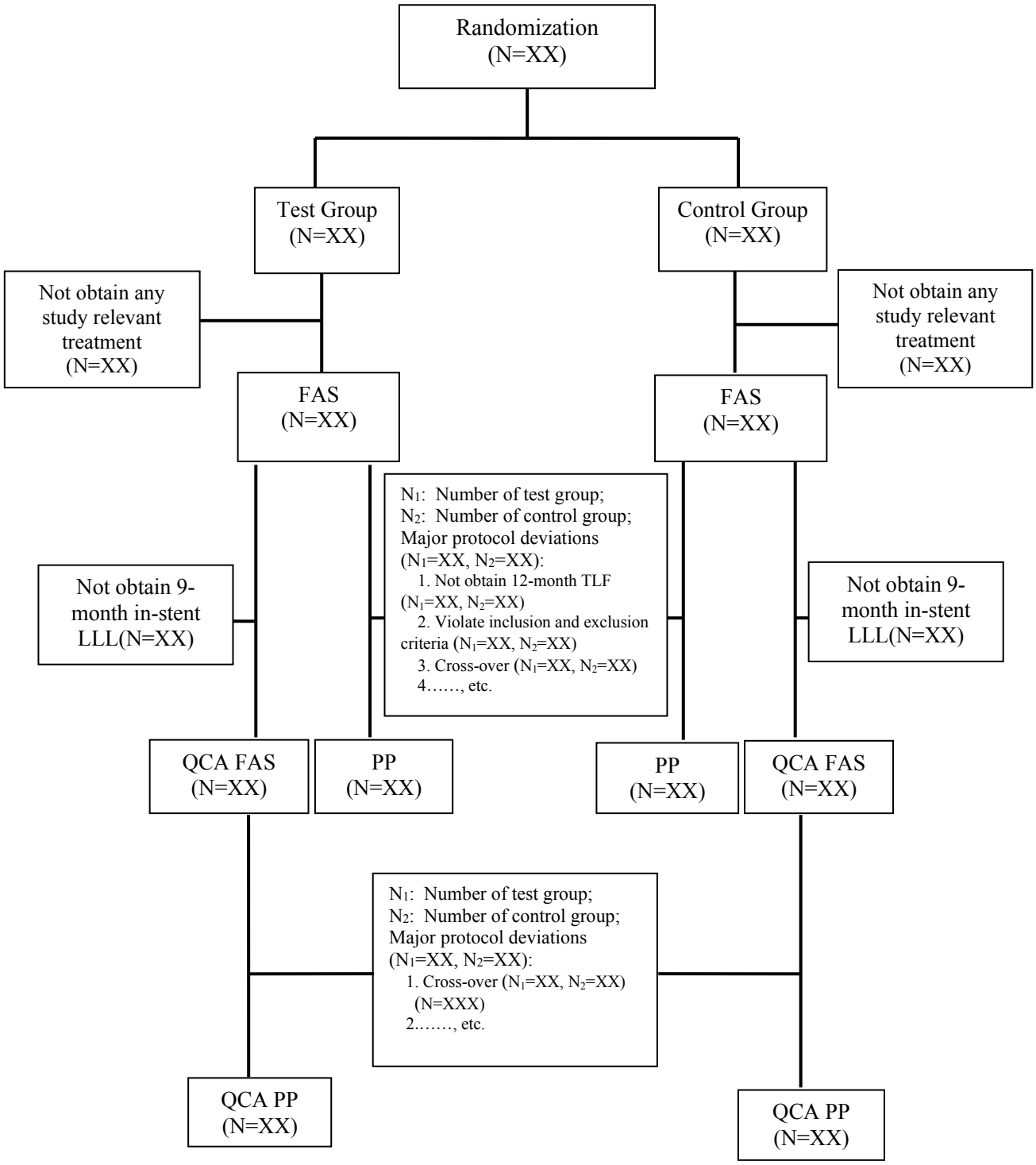

Figure 1 Flow Chart of Analysis Population Determination

Note: Test group: Resolute Onyx stent group;
Control group: Resolute Integrity stent group.

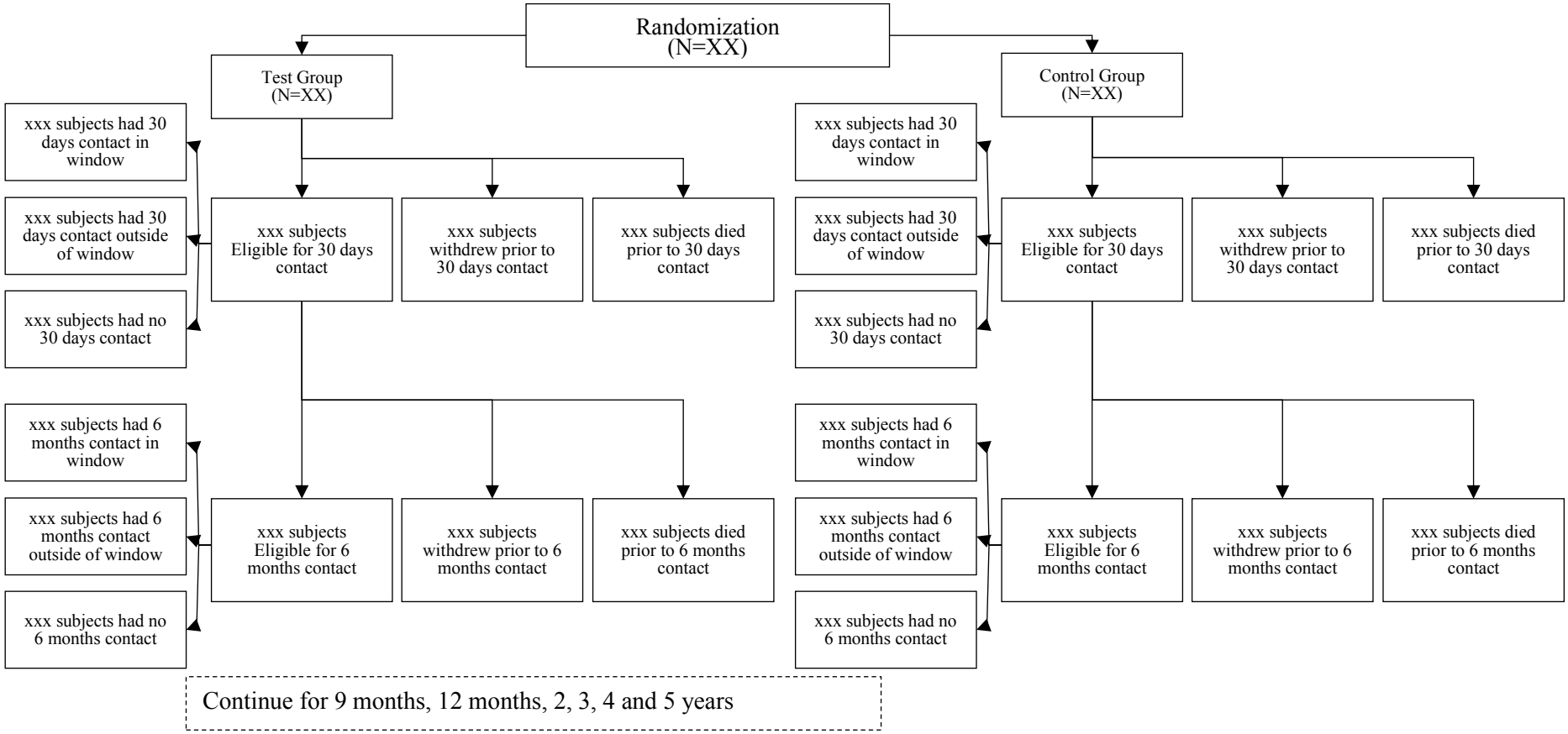

Figure 2: Patient Disposition Flow Chart Post-Procedure – Clinical Follow-up

7.3. ANALYSIS STRATEGY AND GENERAL METHODOLOGY

Non-inferiority test will be assessed for the analysis of primary endpoint. Generalized estimating equations (GEE) and ANCOVA approach will be used for lesion-level and patient-level analysis, respectively. Descriptive statistics will be provided for the analysis of each arm. Comparisons between arms will be presented with differences (with 95% Confidence Intervals) and P-values.
All statistical analyses will be performed with two-sided 0.05 significant level unless otherwise specified. Statistical software SAS® 9.4 or higher will be used. Subject data listings and tabular and graphical presentations of results will be provided.
All analyses will be based on FAS, unless otherwise specified. For clinical events, the numerator of the event rate will be the number of "FAS" subjects having an event before the time of interest. The denominator will be the number of subjects who either have an event by the time of interest, or have follow-up information beyond the lower window of the follow-up.
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.
The study pass/fail criteria is based on statistical hypothesis and the final analysis results.

7.4. 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. 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. multiple imputation will be used in secondary analysis.
For missing data related to other measures, no statistical techniques will be used for continuous or categorical characteristics and outcomes.
In time-to-event outcomes, drop-outs will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data. Withdrawal and drop out will not be replaced.
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.
Screening and acceptance testing of these data will be carried out in accordance with Data Management Plan. To this end, all data involved in the determination of endpoints will be screened for missing and unusual values. Any missing data that affect the ability to determine or analyze any endpoint will be queried by Data Management for confirmation of irretrievability. Unusual values, such as outliers, will also be queried, and if confirmed, will be used as recorded.

7.5. ANALYSIS OF THE PRIMARY ENDPOINT

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.
The primary analysis of the primary endpoint will be based on the available data only. i.e. The primary analysis of primary endpoint will be performed on both the QCA FAS and the QCA PP analysis sets.

To account for missing data in the primary endpoint evaluation, multiple imputation will be performed as a secondary analysis. Subjects who do not obtain their in-stent MLD at post procedure or at 9 months angiographic follow up will have their 9 months in-stent late lumen loss imputed using PROC MI in SAS. The covariates to be used in the imputation model are lesion-length, baseline RVD, age, sex, diabetes, history of MI, Canadian Cardiovascular Society Angina Class, and group (Resolute Onyx/Resolute Integrity).
Lesion based characteristics (lesion length and RVD) will be converted to patient-based characteristics prior to the analysis: if a patient had more than one lesion, the longest lesion length and the smallest RVD will be used. CCSC will be analyzed as a binary variable with categories (0,1) as value 0 and (2,3,4) as value 1. If the intervention was not prompted by angina or myocardial infarction (i.e. it was prompted by silent ischemia or positive functional study) then set CCSC as 0.

Prior to multiple imputation, the missing values in the covariates will be imputed first. For continuous variables, the missing values will be imputed as MU+sqrt(S2)*rannor(seed), where MU denotes the sample mean of the specific continuous variable, sqrt(S2) denotes the sample standard deviation. If the imputed value is above the maximum value of that variable, the maximum value will be used as the imputed value; if the imputed value is below the minimum value of the variable, the minimum value will be used as the imputed value. For binary categorical variables, the missing values will be imputed as RANBIN (seed,n,p), where n=1, p denotes the observed proportion of the specific binary baseline variable in each arm. The seed will be set as 10000.

One hundred imputed data sets will be generated using regression method (REG option in PROC MI). PROC MIANALYZE in SAS will be used to summarize the overall treatment difference, standard error, and two-sided 95% confidence interval, and will be compared to the pre-specified non-inferiority margin.
The above secondary analysis on the primary endpoint will be performed on both the QCA FAS and the QCA PP analysis sets.
If the non-inferiority of in-stent late lumen loss is demonstrated and a numerically smaller in-stent late lumen loss is observed in Resolute Onyx China RCT, a superiority analysis will be performed by using the same analysis approach as non-inferiority test.
Specifically, the null and alternative hypotheses are:

H_0: $\mu_A \geqslant \mu_C$

H_1: $\mu_A < \mu_C$

7.6. ANALYSIS OF SECONDARY ENDPOINTS

For the secondary endpoints, treatment difference, 95% confidence interval of the treatment difference and p-value will be provided. P-values will be based on Chi-square test with continuity correction or Fisher's exact test for categorical outcomes, and two-sample t-test for continuous outcomes. The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot, with differences between groups for such variables tested by log-rank tests. For the myocardial infarctions (MI) component of the endpoints, the extended historical MI definitions will be used if no specification is provided.

7.7. ANALYSIS OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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.

7.8. EFFECTIVENESS ANALYSIS

For the primary endpoint, both the lesion and patient level analysis will be done for 9–month in-stent late lumen loss (LLL). To account for the cluster effect, the generalized estimating equations (GEE) will be used on lesion level analysis. The PROC GENMOD in SAS will be used with center and baseline effect (intraoperative immediate minimal lumen diameter) adjustment. For patient level, the comparison between two groups will be presented by using the ANCOVA analysis with adjusting center and baseline effect (intraoperative immediate minimal lumen diameter). The interaction term between center and treatment group will be excluded from above models if P for interaction was not significant. If a patient had multiple lesions, one lesion will be randomly selected from multiple lesions for patient level analysis. The two-sided 95% confidence intervals (CIs) of the difference on LLL between groups will be estimated for both lesion and patient level. Other effectiveness endpoints will be analyzed using similar method as baseline analysis.

Additionally, the corresponding details of randomly selecting lesion for patient level analysis if a patient had multiple lesions are as following:

1) At first, the data will be sorted by subject unique identifier number, then lesion sequence number will be generated for each lesion of each patient.
2) The total number (N) of lesions for each patient will be calculated. We will divide [0,1] into N intervals. i.e. each interval length will be 1/N.
3) A random number will be generated according to (0,1) uniform distribution for each patient by ranuni(seed) in SAS. The seed will be set as 10000.
4) Which interval is the random number contained in, the corresponding sequence number lesion will be selected for patient level analysis. If the random number is equal to 1, then the maximum sequence number lesion will be selected for patient level analysis.

7.9. SAFETY ANALYSIS

Adverse event will be reported with event counts and percentages. Meanwhile, the symptom, severity and the relation to investigational devices of all adverse events will be described in a detailed manner.

7.10. ANALYSIS OF SUBGROUPS

Subgroup analyses will be performed on specific subject subsets, like subjects with specific demographics, clinical indications and/or lesion or vessel characteristics. For each of the subgroups below, principal safety and effectiveness results will be provided. More subgroups analysis, demographic and baseline characteristics, and baseline angiographic characteristics can be provided if need.

- Male
- Female
- Age ≥ 65
- Diabetes
- Non-Diabetes
- Long lesion (with at least one lesion length ≥30mm)
- Small vessel (with at least one RVD≤2.5mm)
- Single vessel
- Multiple vessels
- Single lesion
- Multiple lesions
- Overlapping
- Bifurcation

8. VALIDATION REQUIREMENTS

All the output of analysis described above need to be validated by independent biostatistician and/or SAS programmer and all the output can be available to be delivered as long as validated.

9. APPENDICES

APPENDIX I: INCOMPLETE DATE OF AE ONSET

The table below is guiding on how to input missing dates for AE onset

Valid Portion	Missing Portion	Imputed Value for missing Portion
Month, Year	Day	Set Day = first day of that month and year, then set the day = later of (New onset date, procedure date).
Year	Day, Month	Set date = later of (January 1st of that year, procedure date).
None	Day, Month, Year	Date of Procedure

APPENDIX II: FOLLOW-UP VISIT WINDOWS FOR ENDPOINT ANALYSES

Follow-up interval	Study Time Window Post Procedure
30 days	30 ±5 days
6 months	180 ±14 days
9 months	270 ±30 days
12 months	365±30 days
24 months	730 ±30 days
36 months	1095 ±30 days
48 months	1460 ±30 days
60 months	1825 ±30 days

Appendix III: Subject follow-up window

Follow-up interval	Window
30 days	30 days post-implant ±5 days
6 months	6 calendar months ±14 days
9 months	9 calendar months ±30 days
12 months	12 calendar month ±30 days
2 years	2-year anniversary ±30 days
3 years	3-year anniversary ±30 days
4 years	4-year anniversary ±30 days
5 years	5-year anniversary ±30 days