Rotational Atherectomy Combined With Cutting Balloon to Optimize Stent Expansion in Calcified Lesions (ROTA-CUT)
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Rotational atherectomy combined with cutting balloon to optimize stent expansion in calcified lesions

ROTACUT

STUDY PROTOCOL

Protocol Number: CICR-001-ROT
Version: 11
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Sponsor:

The Icahn School of Medicine at Mount Sinai

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1 PROTOCOL REVISION HISTORY

Protocol Revision Number	Protocol Revision Date	Change details
3.0	15 JAN 2021	Initial release
4.0	15 Feb 2021	Response to FDA
5.0	18 Feb 2021	Response to FDA – addition of risk mitigation strategy for trial
6.0	19 FEB 2021	Response to FDA - Addition of Investigator Agreement requirements
7.0	22 Feb 2021	Addition of secondary endpoints and inclusion/exclusion criteria clarification
8.0	22 Jun 2021	Correction of typographical errors Page 18 - 7.3.3 Intravascular Ultrasound Assessment Addition of clarification regarding safety measures associated with the final IVUS run and blinding of the interventional cardiologist Page 19 –8.2 Correction of Troponin T to Troponin I as per CRFs Page 25 – 11.8 Stopping rules: Addition of stopping rules Page 31 - 12.5 – Medical Monitor: Addition of a Medical Monitor Page 31 –Clinical events committee adjudication is now section 12.6, previously 12.5 Page 37 - Addition of References
9.0	17 Aug 2021	Response to FDA: Page 25 – 11.8 Stopping rules: Clarification on Stopping Rules Page 31 – 12.6 Clinical events committee adjudication: Clarification Page 32 - 13.3 Clinical events committee: Clarification
9.1	17 Aug 2021	Response to CMS office: Page 14 – 6.4.2 SECONDARY ENDPOINTS: Clinical endpoints assessment at 30 AND 270 day follow-up; Addition of CCS Class assessment Page 15 – 7.2 7.2 Schedule of assessments: Addition of CCS class Page 19 - 8.3 30-day & 270 day Follow-ups: addition of angina status and CCS class Page 25 - 11.5 Anticipated Benefits: Clarification Other Changes Correction of typographical errors Page 15 – 6.5 Screening, Enrollment, and Randomization: Clarification of Randomization Page 25 - 11.7 Justification of Trial– Addition of References
9.2	17-Nov-2021	Response to FDA: Page 25 – 11.8 Stopping rules: Clarification on Stopping Rules
10	10-Nov-2022	Update to Investigator Information Page 11 - 6.2 Number of Subjects and Clinical Sites: Update to site enrollment allotment Page 33 - 13.5.2 MONITORING: update to source data verification for 30 and 270 day Follow-up Correction of typographical errors
11	02-Mar-2023	Page 11 - 6.2 Number of Subjects and Clinical Sites: Update to site enrollment allotment

2 PROTOCOL SIGNATURE PAGE

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Name: _____ **Title:** _____

PRINCIPAL INVESTIGATORS

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3 TRIAL KEY CONTACT INFORMATION

3.1 Sponsor and Principal Investigator contact details

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
Cath Lab	Cardiac Catheterization Laboratory
CVA	Cerebrovascular accident
DES	Drug-eluting stent
EEM	External Elastic Membrane
DM	Diabetes Mellitus
HIPAA	Health Insurance Portability and Accountability Act
ISMMS	Icahn School of Medicine at Mount Sinai
MACE	Major Adverse Cardiovascular Event
MI	Myocardial Infarction
NSTEMI	Non-ST Elevation MI
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PI	Principal Investigator
RA	Rotational Atherectomy
ST	Stent thrombosis
STEMI	ST Elevation MI
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target lesion revascularization
TVR	Target vessel revascularization
UA	Unstable Angina

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

Patients undergoing percutaneous coronary intervention (PCI) for calcified lesions experience a high rate of major adverse cardiovascular events, including in the contemporary drug-eluting stent era.(1-3) Rotational atherectomy (RA) is an established tool in interventional cardiology for treatment of calcified coronary lesions.(4) The primary rationale for use of RA is to modify physical attributes of calcified plaque to facilitate balloon angioplasty and stent deployment. Although RA is recommended for plaque preparation in severely calcified lesions, a large number of patients demonstrate high residual stent diameter stenosis after RA and stent implantation resulting in similar restenosis rates and major adverse cardiac event (MACE) between patients treated with and without RA.(5, 6) Several clinical trials showed no benefits with aggressive strategy for procedural success or target vessel revascularization.(7) The study hypothesis is that calcified lesion preparation with rotational atherectomy followed by cutting balloon angioplasty (ROTA + CUT) will result in increased lumen gain, more optimal stent expansion and decreased MACE compared to rotational atherectomy followed by plain old balloon angioplasty (ROTA + POBA) in patients with calcified lesions.

4.2 Study Devices

Model	Manufacturer	Region	Status
ROTAPRO ™	Boston Scientific	Global	Commercially Available
Wolverine ™ Coronary Cutting Balloon Monorail & Over-the-wire	Boston Scientific	Global	Commercially Available

4.3 Compliance Statement

This study will be conducted in full accordance with all applicable Federal and State laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented.

The Principal Investigators will perform the study in accordance with the protocol, and will report any unexpected problems in accordance with applicable IRB Policies and Procedures and all Federal requirements.

5 STUDY OBJECTIVES

The aim of the study is to compare the effect of two lesion modification strategies, ROTA+CBA and ROTA+POBA for the treatment of obstructive calcified lesion on minimum lumen area (MLA), stent expansion and apposition obtained with IVUS, procedural- and short-term clinical outcomes. The primary endpoint will be post-procedural Minimum Stent Area (MSA, mm^2) assessed by IVUS.

The secondary aim of the study is to assess the IVUS and quantitative coronary angiography (QCA) parameters both acute post device and final (post stent and post dilatation) between the ROTA+CBA and ROTA+POBA arms. Further secondary endpoints will include percent stent expansion and stent strut malapposition, procedure related complications, and 1 & 9 - month MACE among the list.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a prospective, multi-center randomized pilot study of 60 patients with stable CAD undergoing PCI for a *de novo* calcified lesion with drug eluting stent implantation. Patients with target vessel reference diameter of ≥2.5 mm and ≤ 4.0mm, lesion length ≥ 5 mm and moderate to severe calcification confirmed by angiography will undergo pre-procedural IVUS assessment, if feasible. Subjects with moderate or severe calcification for at least 5 consecutive mm in a *de novo* lesion, confirmed by angiography, will be enrolled. Enrolled subjects will be randomized in a 1:1 fashion to either ROTA + CUT or ROTA + POBA group. Rotational Atherectomy will be performed using Burr: Artery ratio of 0.4 to 0.6 in both arms. Intra-procedural IVUS pullbacks will be performed after lesion preparation, prior to stent implantation and after stenting. Upon PCI completion, operators will be blinded to final, post angioplasty IVUS results. An unblinded physician will review the results of this final IVUS run for safety signals not present on fluoroscopy. All patients will receive a drug-eluting stent after plaque preparation.

6.2 Number of Subjects and Clinical Sites

The pilot study of 60 patients will take place at Mount Sinai Hospital (Dr. Sharma) and St. Francis Heart Hospital (Dr. Moses) with up to 48 patients enrolled at each site. All study subjects will sign an informed consent.

6.3 Study Population

Patients ≥18-years-old undergoing PCI for a *de novo* calcified lesion with planned drug-eluting stent implantation

6.3.1 Inclusion Criteria

A subject who meets ***all the following criteria*** potentially ***may be included*** in the trial:

1) Patient (or legal guardian) is ≥18 years if age and understands the trial requirements and the treatment procedures and provides written informed consent
2) Patient undergoing PCI for a *de novo* calcified lesion with planned rotational atherectomy and planned drug-eluting stent implantation of a lesion with target vessel reference diameter ≥2.5 mm and ≤ 4.0mm, lesion length ≥ 5 mm and moderate to severe calcification by angiography
3) Patient is eligible for PCI
4) Patient is willing and able to comply with all protocol-required follow-up evaluations

6.3.2 Exclusion Criteria

A subject who meets ***any of the following criteria will <u>not</u> be included*** in the trial:

1) Patient in cardiogenic shock
2) Planned surgery (cardiac and non-cardiac) within 6 months after the index procedure unless the dual-antiplatelet therapy (DAPT) can be maintained throughout the peri-surgical period
3) Patient undergoing primary PCI for ST-segment elevation myocardial infarction
4) Subject is pregnant, nursing, or is a woman of child-bearing potential who is not surgically sterile, < 2 years postmenopausal, or does not consistently use effective methods of contraception
5) Patient has any other serious medical illness (e.g., cancer, end-stage congestive heart failure) that may reduce life expectancy to less than 12 months
6) Currently participating in another investigational drug or device study
7) Patient referred to coronary artery bypass grafting after heart team discussion

6.3.3 Angiographic Specific Exclusion Criteria

8) Lesion(s) with angulation > 45 degrees by visual estimate
9) Lesion(s) stenosis through which a guidewire will not pass.

10) Last remaining vessel with compromised left ventricular function (defined as LVEF <30%)

11) Saphenous vein grafts

12) Angiographic evidence of thrombus

13) Angiographic evidence of significant dissection at the treatment site

14) Lesion(s) with previously placed stent within 10 mm (visual estimate)

6.4 Endpoints

The following are the planned study endpoints

6.4.1 PRIMARY ENDPOINT

- Post-procedural Minimum stent area (MSA in mm^2), as assessed by final IVUS (post Stent and post-dilatation).

6.4.2 SECONDARY ENDPOINTS

- IVUS endpoints will be assessed at the following time points
    - Final IVUS (post Stent and post-dilatation)
        - In-segment Minimum lumen area (mm^2), as assessed by IVUS after stent implantation and (optional) post-dilatation, referenced to the EEM
        - Minimum stent expansion (as defined as MSA mm^2), as assessed by IVUS directly after stent implantation and post-dilatation
        - Mean stent expansion (%) –defined as mean stent area divided by the mean reference lumen area, where reference lumen area will be the average of the proximal and distal 10mm to the stent and/or the reference EEM at the site of MSA
        - Any dissection
        - Any malapposition
    - Pre-stent implantation post RA and CBA or POBA
        - Any dissection
        - Assessment of calcium fracture
- Angiographic endpoints measured in both in-stent, injured and in-segment (defined as injured or stent (whichever is larger) plus 5mm either end as feasible)

- Acute lumen gain (mm)
- Final residual diameter stenosis (%)
- Pre, pre-stent, and final minimum lumen diameter (mm)
- Pre-stent and final dissection type B or greater
- Final perforation (Ellis type ≥2)
- Final side branch closure (≥ 1.5mm)

- Device-related endpoints as defined by any problems related to the devices, including but not limited to: balloon rupture, blade detachments, difficulty in withdrawing/advancing the device, or other device related problems as identified by the investigator.
- Clinical endpoints at 30-day and 270 day follow-up:
  - All-cause death (and further classified as cardiac and non-cardiac)
  - Myocardial infarction (as defined by the SCAI definition and Universal definitions, including peri-procedural myocardial infarction)[8,9]
  - Target lesion revascularization
  - Target vessel revascularization
  - Stent thrombosis (definite/probable)
  - Major bleeding (BARC 3 or 5)
  - Vascular complications
  - Target Lesion Revascularization
  - Functional status (according to CCS class)

6.5 **Screening, Enrollment, and Randomization**

All patients who are clinically suitable for treatment with a DES and who meet the study inclusion criteria while not meeting any study exclusion criteria will be approached for inclusion in the study. Subjects who agree to participate will sign an Institutional Review Board (IRB) approved study informed consent and will proceed to the cardiac catheterization lab for further assessment of the angiographic inclusion and exclusion criteria.

If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, randomization will be performed before planned use of rotational atherectomy, but after the guidewire has successfully passed the lesion and the subject will be considered enrolled in the study. Randomization will be an integrated functionality of the EDC.

If the subject fails to meet inclusion/exclusion criteria, s/he will be considered a screening failure and will be excluded from data collection. Treatment of screening failures will then proceed as would occur within the standard of care outside of the study.

6.6 Subject Termination or Withdrawal

Once enrolled, subjects may discontinue participation at any time by withdrawing informed consent or meeting the requirement for termination. Participation in the trial is entirely voluntary. Data from subjects who withdraw from the study will be included in all planned study analyses up until the point of withdrawal or exit. Any subject who is randomized and enters the study procedure but for whom the procedure is abandoned prior to attempted rotational atherectomy will be exited from the study.

7 STUDY PROCEDURES

7.1 Subject Screening and Informed Consent

All subjects who are clinically suitable for PCI treatment with rotational atherectomy and a DES and meet study eligibility requirements will be asked to participate in further screening and will be asked to sign a study-specific IRB approved study consent form prior to angiography.

7.2 Schedule of assessments

Assessment	Inclusion and Baseline	Procedure	Discharge	30 Days (+/-7 d) (Telephone contact)	270 Days (± 21 d) (Telephone contact)
Demographic characteristics	X				
Medical History, cardiac history, and risk factors	X				
Angina status	X		X	X	X
Physical examination[1]	X				
NYHA class	X				
CCS class	X		X	X	X
Laboratory Assessments[2]	X		X[4]		
12-lead electrocardiogram	X		X		
Previous medications	X				
Clinical inclusion/exclusion criteria	X				
Informed Consent	X				
Pregnancy test (if applicable)	X				
Angiography		X			

Pre-procedural IVUS (if feasible)		X			
Inclusion/exclusion criteria		X			
Randomization		X			
Atherectomy +/- CBA		X			
Post-lesion preparation IVUS		X			
Stenting procedure		X			
Postprocedural blinded IVUS		X			
Antiplatelet/antithrombotic medication		X	X	X	X
Adverse Event Assessment		X	X	X	X
Medication changes[3]		X	X	X	X

[1]Physical examination: height and weight (at inclusion only), heart rate and blood pressure. CBA – Cutting balloon atherectomy

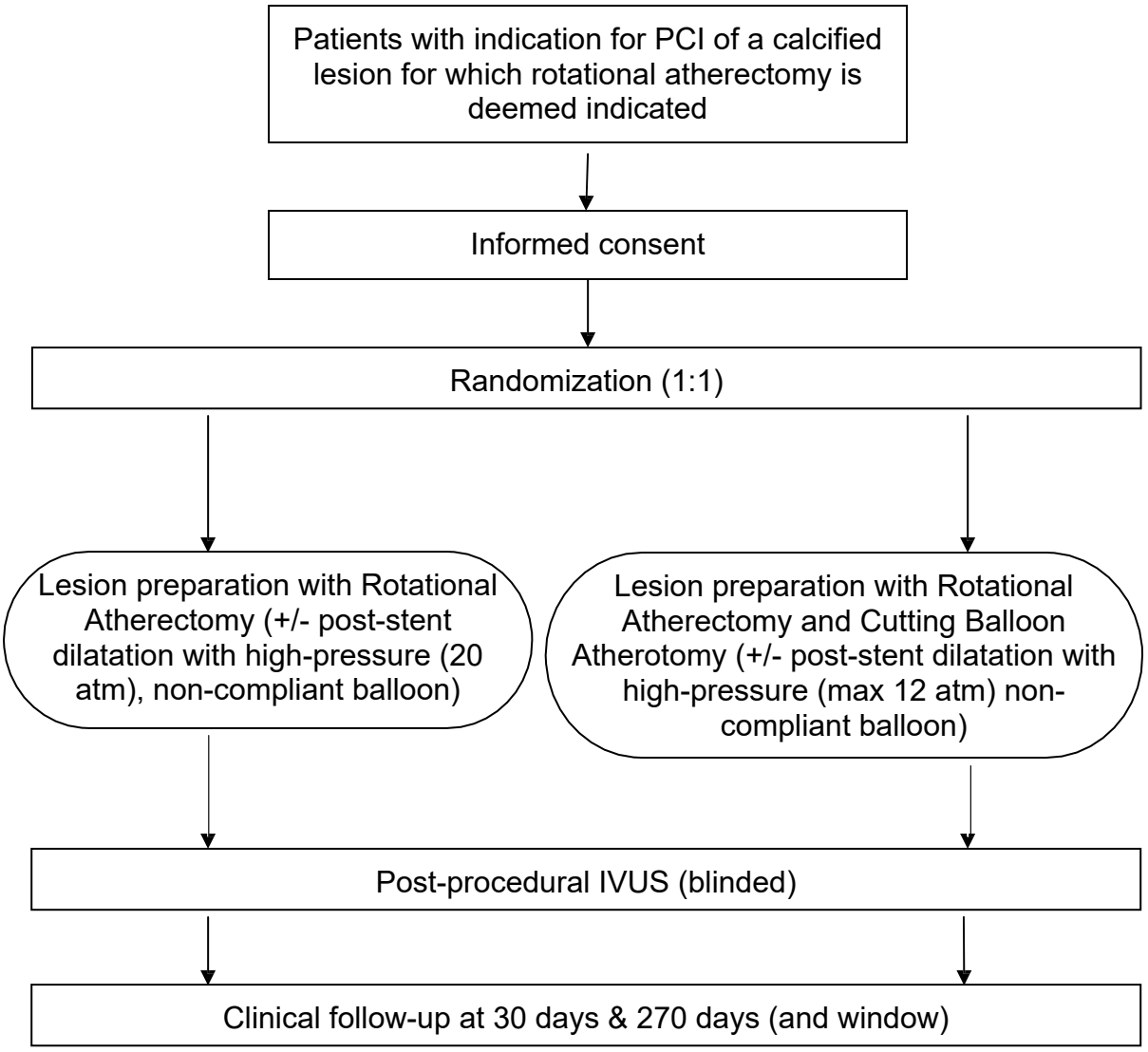
[2]Hematology and blood chemistry, creatinine, and low-density lipoprotein cholesterol

[3]Changes to cardiovascular medications collected only.

[4]In acute patients CK and/or CK-MB or troponin prior to the procedure and in the case of signs/symptoms of myocardial infarction/myocardial ischemia. Laboratory assessments including CK and/or CK-MB or Troponin should be done prior to procedure and at discharge in patients presenting with signs/symptoms of acute coronary syndrome/myocardial infarction/myocardial ischemia. *Patients with STEMI are excluded from the trial (see exclusion criteria 4).

7.3 Procedure overview

7.3.1 Study flow chart



7.3.2 Coronary Angiography

Coronary angiography for off-line QCA analysis will be performed 1) at baseline, 2) after each step of the lesion preparation, and 3) at the end of the procedure. After intracoronary injection of 100-200mcg of nitroglycerine, coronary angiography will be performed in two orthogonal projections aimed to minimize lesion foreshortening and differing at least 30^{o} of rotation. The catheter tip, filled with dye, should be visible for QCA calibration and the lesion should ideally be located in the center of the field of view.

7.3.3 Intravascular Ultrasound Assessment

Intravascular ultrasound assessment for off-line analysis will be performed with the following strategy The 60Mhz OptiCross^{tm} IVUS catheter (Boston Scientific, Marlborough, MA, USA) using automated pull-back at 1mm/s. The catheter will be advanced at least 5 mm distal to the target lesion.

1) at baseline, prior to any intervention, if possible. This IVUS run is optional
2) after lesion preparation defined as RA + POBA or RA + CBA, and
3) at the end of the procedure. This will be following completion of the interventional procedures per the interventional cardiology investigator.

   During the procedure, any additional IVUS runs and assessments deemed clinically indicated by the treating physician to guide the procedure will not be precluded from being performed; these will occur prior to the Final post-angioplasty IVUS run.

   Only after the operator deems the procedure to be finished, will the final post angioplasty IVUS run be performed for endpoint assessment. In order to reduce bias, operators will be blinded to the final IVUS run pullback images and no additional stent placement or post dilation is allowed after the Final IVUS run. Blinding will be performed by either turning the IVUS console results away from the primary investigator in the room, or having the primary investigator turn away, if the former is not feasible.

   To ensure safety, an unblinded physician will be available at the end of the procedure to review the results of the Final IVUS run for safety signals not present on fluoroscopy. If the unblinded physician has any safety-related concerns, the operator will take immediate actions to ensure the safety of the patient.

7.3.4 Rotational Atherectomy (RA) Strategy

Rotational atherectomy will be performed according to the instructions for use and current best practices using a maximum burr-to-artery ratio of 0.4-0.6, a burr speed of 140,000 – 160,000 RPM, and a maximum run duration of 20s. Burr upsizing during the procedure is allowed but the maximum burr-to-artery ratio is not to exceed the recommended 0.6.

7.3.5 Cutting Balloon Atherotomy (CBA) Strategy

In patients randomized to RA+CBA, cutting balloon atherotomy using a Wolverine^{tm} cutting balloon (Boston Scientific, Marlborough, MA, USA) will be performed after rotational atherectomy. The Wolverine cutting balloon will be sized 1:1 relative to the reference vessel diameter and the inflation pressure is recommended at 6 ATM and is expected not to exceed the device rated burst pressure of 12 ATM.

7.3.6 Procedure Strategy

The following procedure strategies should be followed in regard to overall treatment strategy of the study subject:

- Additional lesions may be treated during the same procedure or may be staged according to the discretion of the operator
- Study subjects are to be maintained on dual antiplatelet therapy or oral anticoagulation with single or dual antiplatelet therapy according to applicable guidelines

8 FOLLOW-UP ASSESSMENTS

8.1 Post-procedure Management

Standard of care hospital protocols for the management of patients after treatment with DES shall be followed.

8.2 Discharge Assessment

All subjects shall be discharged from the hospital at the discretion of the attending clinical team. Per the standard of care, and at some time prior to dismissal, all subjects shall undergo an assessment of angina status, a 12-lead ECG, and the following lab assessments: hematology and blood chemistry, CK-MB or troponin I, and creatinine. Subjects who had acute angina prior to the procedure, or experienced any events between the procedure and discharge, will have CK and/or CK-MB or troponin I repeated upon discharge. Changes to cardiovascular medications will be collected at discharge as well as an assessment of adverse events.

8.3 30-day & 270 day Follow-ups

At 30 days (+/- 7 days) and 270 days (+/- 21 days) the patient shall be contacted by telephone at which time information on cardiovascular medication as well as an assessment of adverse events, angina status and CCS class will be obtained.

8.4 **Missed Follow-up**

The Investigator(s) will make every attempt to follow the subjects. All subjects will be encouraged by the Investigator(s) to report any address or telephone number changes to the trial site. Subjects will be informed of the importance of completing the scheduled follow-up telephone calls even if they are not experiencing any medical issues. If a subject cannot be reached for a follow-up visit, or misses a scheduled visit, the visit will be recorded as a missed visit as of the date of last attempted contact. The procedure for attempts at contact should be three phone calls made and recorded in the study medical record plus mailing of a registered letter and contact with the General Practitioner, if allowed per patient consent.

Study subjects exit the trial when no additional follow-up visits, procedures, or data collection are required. A subject is exited from the trial in the following instances:

- Is lost-to-follow-up (LTFU)
- Voluntarily withdraws from the trial
- Death (Cause of death, if available, is to be reported)
- Completes last trial follow-up visit
- Investigator withdraws the subject from the trial

Once a subject has exited the trial, no further follow-up contact will be performed. However, if premature study exit has occurred, vital status may be obtained from public records if allowed by country law.

8.5 **Revascularization, CABG, Death**

In the event of revascularization of the target lesion, or coronary artery bypass graft (CABG), every effort should be made to obtain a copy of the procedure notes as well as any accompanying imaging performed. In the event of the subject's death, every effort should be made to obtain a copy of a death summary/death certificate and any treatment notes. Information on the cause of intervention or death will be reported by the investigator(s) and reported in the study electronic data capture system.

9 ENDPOINT ANALYSIS AND STATISTICAL METHODS

9.1 Analysis Population

The analysis population is the 60 subjects who were enrolled and randomized to treatment with either rotational atherectomy or rotational atherectomy + cutting balloon atherotomy, regardless of procedure outcome. The analysis population excludes subjects who signed the informed consent but who failed to meet angiographic screening criteria (angiographic screen failures).

9.2 Sample Size Rationale

The current study is investigating a novel approach for lesion preparation before stent implantation. As there is limited data available to estimate the expected MSA after rotational atherectomy + cutting balloon atherectomy strategy, no formal sample size calculation was performed. A sample size of 60 patients (total n=60) was chosen for this study. However, a sample size of 60 patients will be powered to detect effect sizes as listed below, given an estimated MSA of 5.50mm^2 ± 2.36mm^2, an equal variance, and a two-sided alpha of 0.05.

Table: Power Calculation

Sample Size	Effect Size (mean difference in MSA)	Power
60	1.6	0.733
60	1.7	0.783
60	1.8	0.828
60	1.9	0.866

9.3 Study Endpoint Testing

9.3.1 Primary Endpoint Hypothesis

Endpoint 1: Minimal stent area (MSA) at the end of the procedure as assessed by IVUS.

The null and alternate hypotheses for the primary endpoint are

H0: Mean MSA^{RA} = Mean MSA^{RA+CBA}

HA: Mean $MSA^{RA} \neq$ Mean MSA^{RA+CBA}

A 2-sided independent samples Student's t-test will be used with a 2-sided alpha of 0.05 to test for differences in MSA between the control (MSA^{RA}) and experimental (MSA^{RA+CBA}) groups.

9.3.2 Secondary Endpoint Testing

Time-to-event analyses using Kaplan Meier methods will be performed for dichotomous clinical secondary endpoint outcomes, event rates in both groups will be compared using the log-rank test.

A 2-sided independent samples Student's t-test will be used with a 2-sided alpha of 0.05 to test for differences in continuous secondary endpoints between the control and experimental groups.

9.4 Descriptive Statistics

Descriptive statistics (arithmetic mean, median as indicated, minimum and maximum and standard deviation) will be calculated for continuous variables. Absolute frequencies and percentages will be obtained for qualitative variables. Summary statistics will be presented according to treatment allocation. 95% Confidence intervals will also be provided.

All statistical tests will be performed with a two-sided alpha of 0.05 and 95% confidence intervals will be presented where applicable, unless otherwise specified.

10 METHODS USED TO MINIMISE BIAS

The following methods are employed to minimize bias in the study:

10.1 Inclusion Bias

All patients eligible for PCI treatment with rotational atherectomy and subsequent DES implantation and who meet the clinical study criteria will be offered participation in the study, pending angiographic assessment of angiographic inclusion/exclusion criteria.

10.2 Endpoint Evaluation

An independent Core Lab will evaluate all study angiograms and all study IVUS runs, and an independent Clinical Events Committee will adjudicate all Endpoint-eligible Serious Adverse Events through the duration of the study.

10.3 Reported Data Veracity

Routine monitoring will be conducted for all reported data according to the study monitoring plan.

10.4 **Avoiding Analysis Bias**

Statistical analysis will be conducted according to a pre-specified Statistical Analysis Plan (SAP).

11 **RISK ASSESSMENT**

11.1 **Potential Risk of the angioplasty and RotaPro procedure**

Given subjects enrolled into this protocol will be slated for angioplasty with the use of RotaPro irrespective of trial inclusion the risks associated with such procedures are presented and reviewed with the patient as a part of the standard of care procedural consent process.

11.2 **Potential Risk of the Wolverine include, but are not limited to:**

- Abrupt closure
- Acute myocardial infarction
- Angina of unstable angina
- Arrhythmias, including ventricular fibrillation
- Arteriovenous fistula
- Cardiac tamponade/ pericardial effusion
- Cardiogenic shock
- Cerebrovascular accident/ stroke
- Coronary aneurysm
- Coronary artery bypass grafting surgery
- Coronary artery spasm
- Coronary vessel dissection, perforation, rupture, or injury, possibly requiring surgical repair or intervention
- Death
- Drug reactions, including allergic reaction to contract medium
- Embolism
- Hemodynamic compromise
- Hemorrhage or hematoma
- Hypo/hypertension
- Infection
- Minor vessel trauma
- Myocardial ischemia
- Percutaneous re-intervention
- Pseudoaneurysm (at vascular access site)
- Pyrogenic reaction
- Renal failure
- Respiratory insufficiency
- Restenosis of the dilated vessel
- Side branch occlusion
- Slow flow/ no reflow
- Thrombosis
- Total occlusion of the coronary artery of bypass
- Transient ischemic attack
- Vasovagal reaction
- Ventricular irritability/ dysfunction
- Vessel trauma requiring surgical repair or intervention
- Volume overload

11.3 **Risks associated with the IVUS procedure**

The IVUS device is designed to function as a conventional, rotating core catheter which has an excellent safety record. Experience with IVUS throughout the world has shown that the catheter safety profile is low with potential adverse events associated with the IVUS in the target lesions at a very low rate (<1%).

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

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

11.4 **Measures to Mitigate Risk to Trial Subjects**

The following measures will be implemented to minimized risk to the trial subjects:

- Treating physicians will have considerable experience with both the Rotational atherectomy device, ROTA PRO, and the wolverine device.
- Treating physicians will have considerable experience with IVUS imaging techniques
- Study sites will have significant experience with severely calcified lesion percutaneous coronary intervention

- Serial IVUS measurements will be performed throughout the procedure as specified above
- Final blinded IVUS runs will be read by an experienced interventional cardiologist before the subject is removed from the catheterization laboratory
- Subjects will be rigorously followed over the course of the trial

11.5 **Anticipated Benefits**

The potential benefit of severely calcified lesion preparation with the combination of rotational atherectomy with the RotaPro followed by a cutting balloon with the Wolverine, is to maximize the final minimal stent area as assessed by IVUS, that would translate in a clinical benefit at follow-up. Indeed, there is ample data supporting that larger stented areas at the end of an angioplasty are associated with lower rates of major adverse event or target vessel failure at long term follow-up. (10, 11, 12)

11.6 **Alternative Therapies**

Presently, therapeutic alternatives for patients meeting the ROTACUT inclusion criteria who are scheduled for PCI rotational atherectomy include the following:

- PCI with rotational atherectomy alone or followed by POBA

11.7 **Justification of Trial**

The treatment of severely calcified lesions continues to have high rates of major adverse cardiovascular events. (1-3) Based upon the literature review presented in the Report of Prior Investigation, the utility of cutting balloon device(s) following successful rotational atherectomy has demonstrated larger post stent implantation MSA as compared to rotational atherectomy and plain balloon.(13-16) This trial is designed to prospectively, and in a randomized fashion, evaluate this treatment strategy. Although there are risks to the subjects for participation in the trial, they are anticipated to be similar to the risks of undergoing PCI for severely calcified lesion outside of the trial. The trial endpoints are clinically relevant for the patient population targeted, those with severely calcified lesions. There are no foreseen differences with regard to sex at birth, age at the time of enrollment with respect to this trial endpoints. Therefore, the trial is justified.

11.8 **Stopping Rules**

A stopping rule based on the occurrence of clinically relevant coronary dissection was defined on the basis of literature review. In previous pilot studies evaluating a strategy of rotational atherectomy with or without cutting balloon, the meta-analytic incidence of coronary dissection was 18% (2-sided 95% upper confidence limit = 28%).(13, 14) Therefore, a stopping rule is set at the occurrence of 11 (18% of 60 patients) flow-limiting coronary dissections leading to a periprocedural myocardial infarction.(17) That is, if during

the enrollment phase, 11 episodes of flow-limiting coronary dissection associated with periprocedural myocardial infarction occur, patient recruitment will be terminated.

If the trial is terminated prematurely or suspended, the sponsor shall promptly inform the clinical investigators and regulatory authorities of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB. The sponsor will, as soon as possible, provide a written statement to the investigators to enable prompt notification of the IRBs. If the trial is terminated early, follow-up visits will continue for all enrolled subjects for the intended length of the study.

12 SAFETY REPORTING

Subjects will be carefully monitored during the study for possible Adverse Events (AEs) from the time of enrollment/randomization to the completion of their participation in the study

12.1 Definitions of Adverse Events and Device Deficiencies

All adverse events shall be will be fully investigated by the Investigator.

Table: Adverse Event Definitions

Term	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 study 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.

Serious adverse event (SAE)	An adverse event that:
	
	• led to a death,
	• led to serious deterioration in the health of the subject, that either resulted in
	  • a life-threatening illness or injury, or
	  • a permanent impairment of a body structure or a body function, or
	  • in-patient or prolonged hospitalization, or

	• medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, • led to fetal distress, fetal death or a congenital abnormality or birth defect 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.
Device deficiency	Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
Device malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.
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
Serious adverse device effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s) UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below: • For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)). • Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after

	the sponsor first receives notice of the effect (§812.46(b), §812.150(b)(1)).
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user NOTE 1: Use error includes slips, lapses, and mistakes. NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

12.2 **Causality Relationship**

Relatedness of the AE to the index procedure or the study device itself will be initially judged by the investigator. For events eligible for CEC adjudication, the CEC will ultimately adjudicate procedure and device-relationship.

Each AE will be classified according to the following levels of causality:

1) **Not related**: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;

- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) **Possible:** the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably have explained by another cause, but additional information may be obtained.

5) **Causal relationship:** the event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event

12.3 **Investigator Reporting Responsibility**

At each study visit, the Investigator will determine whether any adverse events (AE) have occurred. Adverse events will be recorded in a timely manner on the electronic Case Report Form (EDC System) by the Investigator (or any dedicated site personnel) and will include event start and stop dates, description of event, severity, and relatedness to the index procedure and the study device.

In the event that the EDC system is not in service or is not otherwise accessible, the CRA from the Center for Interventional Cardiovascular Research and Clinical Trials should contact the Sponsor per the Safety Management Plan.

It is understood that complete information about the event may not be known at the time the initial report is submitted. The Investigator should make every attempt to obtain as much information as possible concerning the event and ensure that all additional relevant information that becomes available is also forwarded to the Sponsor immediately after the initial notification (i.e., copy of laboratory exams, MRI or CT imaging, hospitalization reports indicating the SAE). All identifying information must be removed from these supporting documents and instead the site should use the unique subject identifier.

There are certain events (specified below) that if they occur require expedited (within 48 hours of knowledge) reporting by the Principal Investigators.

Following events should be reported as Expedited Events:

- Any Serious Adverse Event
- Any Device Deficiency
- New findings/updated in relation to above reported events

All reported events will be followed until resolution, stabilization or 30 days after the last subject enrolled has completed the trial, whichever occurs first.

12.4 **Safety Reporting**

Depending on the local requirements, or following agreement between both parties, the Pponsor or the Principal Investigators will be responsible for performing safety reporting to the Ethics Committee according to the relevant local regulatory requirements.

The Sponsor or Sponsor designee will report all reportable events to FDA.

12.5 **Medical Monitor**

A Medical Monitor will be available to sites on a 24/7 basis for the duration of the trial to address protocol related medical questions from participating sites and will review all AEs to identify events that require formal reporting measures.

12.6 **Clinical events committee adjudication**

The ROTACUT Study will have an independent Clinical Events Committee (CEC) whose role it will be to adjudicate all Endpoint-eligible SAEs through to the end of 270-day follow-up for final endpoint evaluation as well as device and procedure relatedness. The CEC members will be blinded to the subjects' treatment assignments to avoid potential bias throughout the course of the study. All CEC activities and the detailed adjudication process are regulated by the CEC Charter.

13 **TRIAL AND DATA MANAGEMENT**

13.1 **Angiographic Core Lab**

The ROTACUT Angiographic Core Lab is responsible for independently evaluating all procedure angiograms submitted by trial sites. The purpose of the Core Lab is to ensure unbiased, timely and consistent analysis of the diagnostic data, and for evaluating clinical events in subjects over the life of the study.

Angiograms will be sent directly from the investigational sites to the Core Lab via an online image upload portal.

13.2 **Intravascular Ultrasound Core Lab**

The ROTACUT IVUS Core Lab is responsible for independently evaluating all procedure IVUS runs submitted by trial sites. The purpose of the Core Lab is to ensure unbiased, timely and consistent analysis of the diagnostic data, and for evaluating clinical events in subjects over the life of the study.

IVUS runs will be sent directly from the investigational sites to the Core Lab via an online image upload portal or manual delivery.

13.3 Clinical Events Committee

The ROTACUT Clinical Events Committee (CEC) is an independent adjudicating committee which conducts ongoing review of all potential endpoints. The CEC consists of physicians with specialty in cardiology and/or interventional cardiology, who are impartial, independent of the investigator(s) and who have no financial, scientific, or other conflict of interest with the trial. The activities of the CEC along with the definitions and detailed process are described in the CEC Charter.

13.4 Protocol Deviations

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol. The Investigator is not allowed to deviate from the study protocol except to protect the rights, safety and well-being of human subjects under emergency circumstances.

Deviations shall be reported to the trial Sponsor regardless of whether medically justifiable or taken to protect the subject in an emergency. Investigators will adhere to procedures for reporting trial deviations to FDA and IRB in accordance with the applicable laws and regulations.

For reporting purposes, deviations are classified as major or minor:

13.4.1 Major deviations

A major protocol deviation (PD) or noncompliance is one that may have a significant impact on subject safety orwell-being, the subject's willingness to participate in the study, or that may compromise the integrity of the study data and analysis. Examples include:

- Subject enrolled and randomized not having met eligibility criteria at the time of implant/treatment.
- Informed Consent not signed or signed after the initiation of non-standard of care, research related assessments.
- Reportable Safety Event not reported to IRB/Sponsor within the required timeframe

13.4.2 Minor deviations

A minor protocol deviation or noncompliance is unlikely to have a significant impact on subject safety, wellbeing, or is unlikely to compromise the integrity of the study data and analysis.

NOTE: Information that is not essential to the trial endpoints is not considered a deviation if absent.

13.5 **Study Conduct, Training, Monitoring Responsibilities & Confidentiality**

The study is conducted in accordance with Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and this protocol. The study Investigators are responsible for obtaining the appropriate regulatory approvals (e.g., IRB) prior to initiation of the study. The Investigator provides current copies of the study protocol to all sub-Investigators or other staff responsible for study conduct.

13.5.1 Site Initiation and Training

Site staff will be trained and experienced in performing their delegated tasks. Training may be in person, webinar, read and review, or other methods as deemed appropriate.

Training is documented on an "Individual Training Log". A "Delegation of Authority Log" is completed at each site for all trial staff individual designating which specific clinical trial related tasks may be performed. The delegated tasks will determine what the training requirements are for each member of the trial support staff. Technicians performing the angiograms do not require any additional training to perform the trial tests, as the requested procedures are standard clinical exams used in standard practice.

New research staff members may be trained by previously trained personnel on the study protocol and procedures, as long as appropriate documentation of that training is completed.

13.5.2 MONITORING

The Center for Interventional Cardiovascular Research and Clinical Trials, or its designee, will conduct site monitoring in accordance with the detail below to ensure that all Investigators are in compliance with the protocol.

The following data will be verified by either in-person, on-site review or virtual visits ensuring adequate review of source data for verification.

Inform Consent	100%
Inclusion/ Exclusion	100%
Serious Adverse Event(s)	100%
Remaining data fields from enrollment to hospital discharge	3 patients or 10%, whichever is higher, randomly selected within each site
30 day and 270 day follow	2 patients or 10%, whichever is higher, randomly selected within each site for both 30 day and 270 day follow up

13.6 **Subject Authorization and Confidentiality**

Subject authorization and written informed consent must be obtained prior to the subject's enrollment into the study and in accordance with GCP, the Medical Devices Directive and

all other applicable standards, regulations (local and national), guidelines and institutional policies. Subject confidentiality must be maintained in accordance with GCPs, HIPAA, and all other applicable standards, regulations (local and national), guidelines and institutional policies.

13.6.1 Investigator Confidentiality

Study Investigators must comply with the applicable provisions of the study Investigator Agreement with regard to nondisclosure and confidentiality.

13.7 **Documentation Requirements**

13.7.1 Source documents

Clinical regulations require that Investigators maintain information in the clinical trial subject's medical records that corroborates data collected on the eCRF. Some examples of critical information to be maintained for possible review by regulatory inspectors are:

- Medical history and physical condition of the subject before involvement in the clinical trial sufficient to verify protocol entry criteria
- Dated and signed notes in the subject's medical record on the day of entry into the clinical trial
- Dated and signed notes, and test reports, from each clinical trial visit with reference to the eCRF for further information, if appropriate (for specific results of procedures and exams).
- Notes regarding concomitant cardiac/diabetic medications taken during the clinical trial
- Subject's condition upon completion of or withdrawal from the clinical trial

To protect subject confidentiality, the subject's name must not appear anywhere on the source documentation or angiographic imaging sent to trial Sponsor, CEC, or Core Lab. All subject identifiers (i.e. medical record number) are to be obscured. Original copies of all data must be kept at the site.

13.7.2 Trial documents

The trial Sponsor will provide pre-printed or electronic forms to each trial site for documentation of:

- Investigator and site training to the protocol (Individual/Group Training Log)
- Financial Conflict of Interest (All Investigators)
- Investigator Agreement required by 21 CFR 812.20(b)(5) (All Investigators)
- Authorized trial site personnel (Delegation of Authority)
- Investigator and site training of EDC utilization (EDC/CRF Training Log)

- Subject consent and screening (Screening and Enrollment Log)
- Monitoring Visit tracking (Site Visit Log)

The site visit is recorded on the appropriate site visit report sent to the Sponsor. During the course of the study, all correspondence regarding the trial must be maintained in the regulatory binder provided by the trial Sponsor. This regulatory binder must be made available for possible audits.

13.8 **Data Collection**

All required data for this trial are to be collected with standardized electronic Case Report Forms (eCRF) for individual subjects**.** If for any reason an eCRF is unavailable and/or inaccessible, a paper CRF will be provided by the trial Sponsor to be completed, signed by the Principal Investigatoror designee and submitted to the trial Sponsor.

13.9 **Data and Document Retention**

Trial-related correspondence, subject records, consent forms, and source documents are to be maintained on file by the trial site. The trial Sponsor requires that it be notified in writing if the Principal Investigator wishes to relinquish ownership of the data and information so that mutually agreed upon arrangements can be made for transfer of ownership to a qualified entity. Records of each subject's participation in the trial must be maintained for no less than a period of two (2) years after trial closure and submission of the final report to the IRB, or longer as dictated by local regulations.

13.10 **Trial Completion**

A final clinical report shall be compiled once data collection is complete. Such reports include all information required and outlined in this protocol. The final report will be provided to IRBs and other regulatory agencies as per applicable laws. The final clinical report will be filed in the trial master file.

13.11 **Future Plans**

No changes are planned at this time.

14 **STATEMENTS OF COMPLIANCE, CONFIDENTIALITY AND RESPONSIBILITIES**

14.1 **Good Clinical Practice Statement**

This trial will be conducted in compliance with all applicable regulations. The protocol and supporting documents for this trial will be reviewed and approved by both FDA and an appropriately constituted IRB prior to trial initiation. All reviews and approvals will be in accordance with Good Clinical Practice (GCP) and all other applicable standards, regulations (local and national), guidelines and institutional policies.

14.1.1 Protection of subject confidentiality

Subject confidentiality will be maintained in accordance with GCP, HIPAA, and all other applicable standards, regulations (local and national), guidelines and institutional policies.

14.2 **Applicable Regulations and Guidelines**

The applicable regulations must be observed to comply with the trial Sponsor's policy for conduct of clinical studies; they represent good clinical practice. It is the responsibility of the investigator(s) and the study Sponsor to comply with the requirements set forth in their country specific regulations.

14.3 **Investigator Responsibilities**

The trial Investigator(s) will adhere to the trial protocol, Good Clinical Practice, HIPAA, and compliance with applicable government and institutional regulations. The trial Investigator(s) is responsible for obtaining proper regulatory approvals and reporting to regulatory authorities per all applicable regulations.

The Investigator is responsible for ensuring that this clinical trial is conducted according to the Clinical Trial Agreement, Protocol, all conditions of regulatory and IRB approval and applicable regulations. Written IRB approval of the protocol and consent forms must be provided to the Sponsor prior to the enrolment of any subject in the clinical trial at each site. The Investigator is responsible for ensuring that informed consent is obtained from all subjects prior to any diagnostic tests or treatments that are outside the standard course of treatment that would be followed if this subject was not being considered for enrolment in this clinical trial. Periodic reports should be provided to reviewing boards and protocol deviations reported per institution's IRB policy.

Subjects must be informed that their medical records will be subject to review by the Sponsor, its authorized designee or regulatory agencies. Subjects shall be made aware that their de-identified data may be made available to the device manufacturer for regulatory submission purposes. Subjects will be informed that they are free to refuse participation in this clinical trial without loss of benefits to which they are otherwise entitled, and, that if they choose to participate, they may withdraw at any time without prejudice to future care. The informed consent will be provided by each site's IRB and consent must be obtained by the subject. The original signed informed consent for each subject must be retained by the Investigator and is subject to review by the Sponsor. A copy of the informed consent will be provided to the subject.

14.4 **Sponsor Responsibilities**

The trial Sponsor will adhere to the trial protocol, Good Clinical Practice, HIPAA, and compliance with applicable government and institutional regulations. The trial Sponsor is responsible for obtaining proper regulatory approvals and reporting to regulatory authorities

per all applicable regulations. The Sponsor is responsible for ensuring that this trial will be conducted in compliance with all applicable local**.** The Sponsor will submit progress and final reports to FDA and as applicable to overseeing IRBs.

The Sponsor will provide Investigators with the information and training required to conduct the clinical trial properly and in accordance with the Clinical Investigational Plan (protocol) and any amendments, if applicable. The Sponsor must ensure that IRB approval is obtained and remains current, and that the reviewing boards are informed of significant new information about the clinical trial.

The Sponsor is responsible for the conduct and administration of this clinical trial. These responsibilities include maintaining regular contact with each trial site ensure compliance with this Clinical Investigational Plan and verify that data are reported in a timely manner.

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