Maria Cecilia Hospital
Cotignola

GVM CARE & RESEARCH

Protocol title:

ROBotically assisted PCI in **OSTIAL** lesions:

the **ROB-OSTIAL** study

Version A
23 November 2022

Sponsor

Corindus, Inc. dba Siemens Healthineers
Endovascular Robotics
275 Grove Street,
Newton, MA 02466

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Principal Investigator

Printed name: ROBERTO NERLA
Site: MARIA CECILIA HOSPITAL – COTIGNOLA (RA)
Signature:
Date:

SPONSOR SIGNATURE PAGE

Printed name: Colleen Smith
Title: Clinical Operations Manager, Corindus, Inc. dba Siemens Healthineers Endovascular Robotics
Signature:
Date:

GENERAL INFORMATION

Clinical Study Proposal	
Study Design	Sponsored Study, Prospective, single-center, randomized
Title - Acronym	Robotically assisted PCI in ostial lesions: the **ROB-OSTIAL** study
Sponsor	Corindus, Inc. dba Siemens Healthineers Endovascular Robotics
Funding address	275 Grove Street Newton, MA 02466
Primary Investigator (PI)	Roberto Nerla MD
Institution	Maria Cecilia Hospital – GVM Care and Research Cotignola (IT)
Version	A
Projected Dates of Study	Estimated First patient in: February 2023 Expected Time to Complete Enrollment: August 2024 (18 months) Expected Time of each Subject to Complete the Study: 1 month Total Expected Duration of the Study: 21 months Estimated study end: November 2024
GCP Statement	The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Good Clinical Practice as well as regulatory requirements
Confidential	This protocol is the property of the Sponsor and may not – in full or in part – be passed on, reproduced, published or otherwise used without permission

* ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

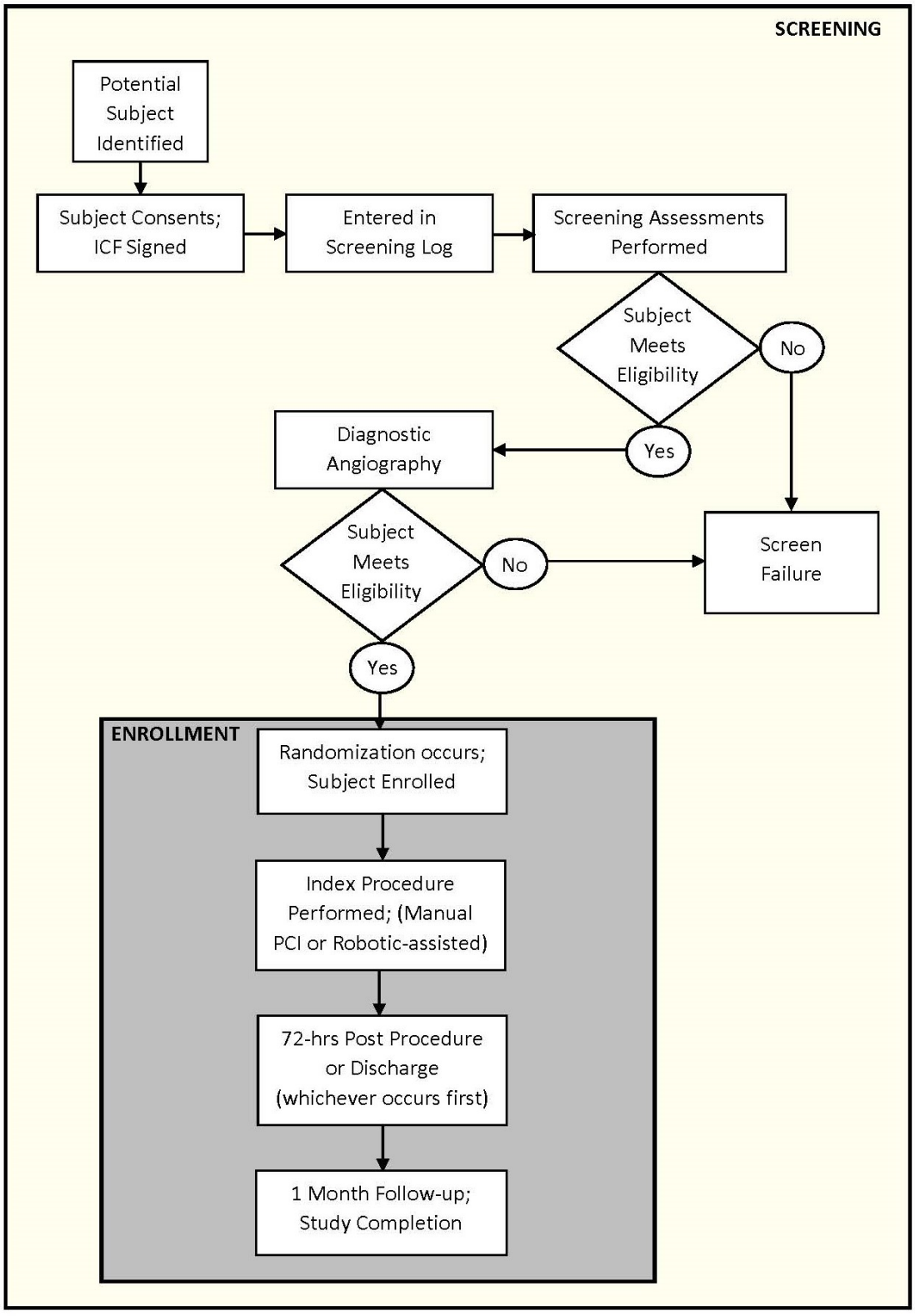
SYNOPSIS

Research Topic:	Robotically assisted PCI in ostial lesions: the **ROB-OSTIAL** study
Summary of Proposal:	To assess accuracy of robotic-assisted PCI in obtaining full ostial lesion coverage and minimal protrusion compared to manual PCI. Robotically assisted PCI offers the opportunity of performing minimal device movements (up to a minimum of 1 mm) in a stable and reproducible setting. This feature may be of great help when dealing with ostial lesions, whose treatment requires a precise stent positioning to avoid strut protrusion but also geographic miss of the lesion. Robotic-assisted PCI for ostial lesions showed encouraging results in large observational registries, but no study compared this approach with manual PCI. We aim to perform a randomized (1:1) study comparing manual (n=33) and robotic-assisted PCI (n=33) in obtaining full lesion coverage when treating ostial lesions (ostial left main will be excluded). Primary endpoint of the study will be full ostial coverage as assessed by IVUS imaging, while secondary endpoints will be procedural success, vessel damage and number of protruding struts in the donor vessel as assessed by IVUS imaging.
Summary of Timeline:	Starting in 2023 (after EC approval), approximate duration 21 months

STUDY TABLE OF ASSESSMENTS

Assessment	Enrollment	Procedure	Discharge	1M FU (± 7 days)
Eligibility criteria	X	X		
Informed consent	X			
Medical and Cardiac history	X			
Canadian Cardiovascular Society (CCS) Angina Grade	X		X	X
Hemoglobin/hematocrit	X			X
CK and/or CK-MB and troponin	X		X	
Total Cholesterol	X			X
Creatinine and Glomerular filtration rate	X		X	X
12-lead ECG	X		X	X
Concomitant Therapy	X		X	X
Procedure: Coronary angiography		X		
Procedure: Percutaneous Coronary Intervention (PCI)		X		
Procedure: Intravascular Ultrasound (IVUS)		X		
MACE - MAE			X	X
Adverse event		X	X	X

STUDY FLOW CHART



1. RATIONALE

Robotic PCI is known to reduce geographical miss of coronary lesions and increase accuracy of stent placement during coronary PCI. Its role may be particularly helpful when treating ostial lesions, which require a precise stent positioning in order to reduce long-term clinical events.

1.1 Clinical need

Accurate placement of coronary stents in ostial locations is known to be challenging (1). Angiographic ostial location ambiguity, often requiring multiple views, and problems with the motion of the stent before deployment are considered possible relevant sources of mistakes during PCI (2). Advancement of the stent past the ostium can lead to ''geographic miss'' where suboptimal scaffolding of the plaque or lack of coverage of areas exposed to balloon injury increase the risk of restenosis (3-5). If the stent is protruding in the donor vessel, it may cause difficulties, including 1) The need to re-cannulate the coronary artery, 2) a possible re-wiring through the side of the stent (in case of re-intervention) with subsequent stent deformation, and 3) unopposed struts undergoing an irregular process of endothelialization and neointima coverage (6,7). Of note, a retrospective analysis of 100 consecutive PCI of aorto-ostial lesions observed stent misplacement (defined as a stent deployed > 1 mm from the ostium) in 54% of cases, of which proximal and distal misses were equally represented (8). Interestingly, a geographic miss was associated with higher rates of restenosis and target lesion revascularization (TLR) compared with ‘accurate’ stent placement.

The use of robotic PCI is able to offer some advantages compared to manual PCI, including the reduction of longitudinal 'geographic miss' and the possibility of performing 1-mm accommodations in device positioning. In addition, it can improve lesion length evaluation as previously reported (9). The adjunct role of robotic-PCI in improving lesion coverage during ostial vessels PCI has never been previously evaluated.

1.2 Device Description

The CorPath® GRX System is intended for use in the remote delivery and manipulation of coronary or peripheral guidewires, rapid exchange (RX) devices and guide catheters during percutaneous coronary intervention (PCI) procedures.

The complete CorPath GRX System includes the following major components:

The Bedside Components consist of an Extended Reach Arm, Robotic Drive and Single-use Cassette. The Extended Reach Arm is mounted on a bed rail and supports the Robotic Drive.

- **Robotic Drive:** Receives inputs from the Control Console. These inputs actuate mechanical operations in Single-use Cassette as movements to a loaded guidewire, RX device, and guide catheter. The Robotic Drive moves forward and backwards to advance and retract the guide catheter. A Bedside Touchscreen on the Robotic Drive provides the user interface for bedside operator during system set-up, loading and device exchanges.
- **Single-use Cassette:** Attaches to the Robotic Drive and can be loaded with commercially available guide catheters, guidewires, and RX devices. This

Single-use Cassette advances, retracts, and rotates the guidewire, advances and retracts the RX device, and rotates the guide catheter.

- **Extended Reach Arm:** Mounted on the rail of the procedure table and supports the Robotic Drive.

The Interventional Cockpit houses the Control Console, the X-ray Foot Pedal, and Monitor(s) to display angiographic and hemodynamic data. It is designed to protect the physician from radiation exposure while maneuvering interventional devices.

Control Console: The Control Console enables the physician to remotely manipulate the guide catheter, guidewire, and RX device. The Control Console has a touchscreen and three joysticks: one joystick for RX device manipulation, one for guidewire manipulation, and a third joystick for guide catheter manipulation.

2 STUDY DESCRIPTION

This is Sponsored, prospective, single-center, randomized study. Subjects who meet eligibility criteria are randomly assigned (1:1) to manual PCI (n=33) or robotically-assisted PCI (n=33). In both arms, the final result will be evaluated by IVUS assessment of ostial coverage.

2.1 Endpoints

The aim of this study is to (1) compare ostial coverage and (2) strut protrusion, as assessed by IVUS, between a strategy of robotic-PCI and a strategy of standard

manual PCI in a prospective randomized study including subjects undergoing elective PCI at a single high-volume center.

Primary endpoints:

1) Evidence of full ostial coverage at angiographic and IVUS assessment

Secondary endpoints:

1) Distance from most proximal stent strut and coronary ostium (mm), as assessed by IVUS
2) In-hospital major cardiovascular events
3) Procedural duration (defined as the duration from when the sheath is inserted until it is removed)
4) Major adverse cardiovascular events at 1 month follow-up

2.2 Inclusion criteria

1. Male or nonpregnant female aged ≥18 years
2. Coronary ostial lesions suitable for percutaneous coronary intervention (PCI).
3. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.

2.3 Exclusion criteria

Subject relevant criteria

1. Cardiogenic shock or hemodynamic instability requiring support.
2. ST-elevation myocardial infarction.
3. Ongoing acute renal failure.
4. In the opinion of the investigator, the subject is deemed unsuitable for robotic PCI due to clinical status and/or anatomic characteristics

Lesion relevant criteria

5. Ostial left main disease
6. Chronic Total Occlusion

2.4 Risks and benefits

Indications to PCI, PCI itself, and medical management of subjects will follow scientific evidence and guidelines. Robotically-assisted PCI did not show safety concerns in published studies and is currently conceived as an adjunctive tool to improve PCI accuracy. The potential benefits of robotically-assisted PCI in this specific setting include a better procedural result (IVUS evidence of full ostium coverage with no/minimal protrusion in the donor vessel) with no difference in major short-term outcomes.

All materials employed are currently commercially available and CE marked.

3 STATISTICAL DESIGN

The present study is a prospective, randomized 1:1, single-center study. It is intended for subjects with indications of coronary revascularization and coronary lesions suitable for PCI. Subjects will be randomly assigned to one arm out of two: robotic PCI (n=33) or manual PCI (n=33) in a 1:1 ratio.

Based on previous studies, we estimated an overall incidence of geographic ostial miss of 50%. Assuming that the use of robotic PCI can selectively achieve at least a 70% reduction of the geographic miss, 66 subjects are required to have an 80% chance of detecting, as significant at the 5% level, a 70% decrease of geographic miss from manual PCI to robotic PCI arm.

4 METHODS FOR ASSESSING AND RECORDING DATA

Data will be recorded on individual subjects' case report forms (CRF) within the electronic data capture (EDC) system.

5 DESCRIPTION OF CLINICAL INVESTIGATION RELATED PROCEDURES

5.1 Baseline evaluation, subject enrollment

All patients admitted and evaluated for coronary angiography and potential PCI will be screened at hospital admission for study eligibility by a member of the investigational site's research team that will review the patient's medical history.

At this point and prior to undergoing any study-related procedures, the informed consent must be explained and signed. During the consent discussion, the investigator or his/her designee must fully illustrate all pertinent aspects and risks of the study and related procedures. In particular, the subject must be informed that randomization will only be done after coronary angiography and coronary lesion suitability assessment. No additional procedure will be performed to assess lesion suitability, as the ostial disease will be only defined by angiography The subject will be considered enrolled after the coronary angiography is complete and the subject is randomized.

5.2 Screen Failure

A subject who signs an informed consent form (ICF) and does not undergo randomization will be considered a screen failure and should be treated according to the standard of care.

5.3 Coronary angiography

After a written informed consent form has been obtained, the subject will undergo coronary angiography. If the presence of critical coronary lesions eligible for PCI is confirmed, lesion-related inclusion/exclusion criteria will be checked to go to the next step of randomization.

5.4 Randomization

Once the investigator has determined that the subject and the procedure are eligible based on inclusion/exclusion criteria, the subject will be randomized in a 1:1 fashion to either robotic-assisted PCI or conventional manual PCI. Randomization is completed after the primary operator assesses the coronary lesion(s). Qualified subjects will be randomized to treatment using an Interactive Web-based Randomization System (IWRS). The IWRS will assign treatment arm and will be recorded in the CRF.

5.5 Coronary angioplasty

Coronary angioplasty will be performed according to common practice and to physician choice concerning lesion preparation, stent implantation, need for post-dilatation or adjunctive treatment strategies. In order to reduce possible confounding factors, the same coronary stent (i.e. Resolute Onyx, Medtronic) will be used for all subjects.

In the peri-procedural period, medications will be administered in line with applicable guidelines on PCI. In particular, during the index procedure heparin or bivalirudin will be used alternately as per the hospital standard of care; while GPIIb/IIIa blockers will be left to the discretion of the operator. Accordingly, subjects will be adequately loaded with dual antiplatelet therapy (DAPT).

5.6 Manual Conversion for Robotic-assisted PCI

Unplanned manual conversion (UMC), defined as a disengagement of the robotic drive to use bedside manipulation of either the guide catheter, guidewire, or delivery system and that was due to:

- Inability to navigate to the target lesion as intended, cross the target lesion as intended, treat the target lesion as intended, retract the CorPath GRX system as intended, or other CorPath system device malfunction; OR
- Any clinical condition that requires rapid medical intervention

In the context of this study, a manual conversion will be considered to have occurred if a subject is randomized to robotic-assisted PCI and the operator converts from robotic PCI to manual PCI when treating the ostial lesion(s). In both study arms, non-target lesion(s) (lesions not located in the ostium) may be treated manually or robotically at the primary operator's discretion. Manual conversion can only occur intraprocedural. Reasons for manual conversion should be recorded in the eCRF.

5.7 IVUS assessment

The secondary endpoint for the clinical study will be the distance from the proximal stent edge to the true ostium as measured by IVUS following stent deployment. The aorto-ostium will be defined as the plane at which the coronary artery joined the aorta sinus. Protrusion of the stent beyond this plane (*protruding stent*) as well as the distance between this plane and the most proximal stent strut (*geographical miss*) will be measured. In the case of side branches (left anterior

descending or circumflex) the ostium will be defined as the plane between the side branch emerging point and the carina tip. Protrusion of the stent beyond this plane (*protruding stent*) as well as the distance between this plane and the most proximal stent strut (*geographical miss)* will be measured.

5.8 Drug regimen

Subjects will receive medications as provided by physicians per standard practice, including anti-ischemic and anti-anginal drugs, antithrombotic drugs, and fluid administration according to the subject's general condition (such as cardiac function).

5.9 Post-Procedure

The following data will be collected 72 hours post-procedure or day of discharge, whichever occurs first:

- Classification of Angina
- Creatinine and Glomerular filtration rate
- 12-Lead ECG
- Adverse Events and Serious Adverse Events
- Concomitant Therapy

5.10 Follow-up

The subject will have a follow-up visit at 1 month (± 7 days) post procedure, in which any clinically relevant adverse event will be assessed. In particular, the

incidence of major adverse cardiac events (MACE), including death, myocardial infarction, and target lesion revascularization, will be checked for secondary endpoints evaluation.

5.11 Subject Study Completion

Subject participation in the clinical investigation will conclude upon completion of the 30-day visit. Upon completion of subject participation in the clinical investigation, the subject will return to the standard of care.

5.12 Subject Withdrawal

Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator. Subjects will be requested to specify the reason for the request to withdraw. The investigator must make all reasonable efforts to retain the subject in the clinical investigation until completion of the clinical investigation.

The Principal Investigator has the right to discontinue a subject's participation in the study in the event of an underlying illness, protocol violation, or for administrative or other reasons. Should a subject withdraw, reasonable efforts will be undertaken to obtain and report the completed observations as thoroughly as possible. A complete final evaluation at the time of the subject's discontinuation

should be made. The reason for the withdrawal will be recorded in the case report form.

When subject withdrawal from the clinical investigation is due to an adverse event, the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

In case of subject withdrawal, the site should make documented attempts to schedule the subject for a final study visit prior to study withdrawal. At this final study visit, the subject will undergo assessments scheduled for the closest protocol-mandated follow-up visit (e.g., 72 hours or discharge or 1 month).

When a subject is withdrawn from the study, all study assessments, with the exceptions mentioned above, are immediately stopped. Any data collected prior to withdrawal from the study will be used in descriptive analyses up to the time point of withdrawal, and results from that subject shall be censored from further analyses thereafter.

6 ADVERSE EVENTS AND DEVICE DEFICIENCIES

6.1 Definitions*

**MEDDEV 2.7/3rev. 3 May 2015 ; ISO 14155:2011*

Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory

finding) in subjects, users, or other persons (this is restricted to events related to the investigational medical device) whether or not related to the investigational medical device. This includes events related to the investigational device or the comparator. This includes events related to the procedure involved in the investigational plan.

Serious Adverse Events

An event is considered serious when:

- led to a death,
- lead to a serious deterioration in health that either:
    1. resulted in a life-threatening illness or injury, or
    2. resulted in a permanent impairment of a body structure or a body function, or
    3. required in-subject hospitalization or prolongation of existing hospitalization, or
    4. resulted in medical or surgical intervention to prevent permanent life-threatening illness or permanent impairment to a body structure or a body function,
- led to foetal distress, fatal death or a congenital abnormality or birth defect.

This includes device deficiencies that might have led to a serious adverse event if a) a suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

A planned hospitalization for pre-existing conditions, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

In the case where a device has failed, the Investigator must inform the Sponsor and make every possible effort to have the Sponsor evaluate the device.

Major Adverse Cardiovascular Events (MACE)

Defined as composite of cardiac death, target vessel MI, target vessel revascularization (PCI and/or CABG).

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event.

Unanticipated Serious Adverse Device Effects (USADE):

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

6.2 Reporting

Sites are encouraged to report promptly:

- any SAE

- any Device Deficiency that might have led to a SAE if a) a suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.
- New findings/updates in relation to already reported events

No later than 24 hours after the event or after being informed about the event the SAE CRF form should be completed in the database. Completing the SAE form in the database will automatically trigger an e-mail alert to the monitoring staff.

Reportable events will be reported by the Sponsor, or designee, to the Ethics Committees and to the Ministry of Health (MOH) as per current regulation.

The investigator will promptly report to the Ethics Committee any death, SADE, and/or USADE that occurred at the site.

7 STUDY ADMINISTRATION

7.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the investigator abides by the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP) in the latest version, in the conduct, evaluation, and documentation of the study. A copy of these documents will be provided to the center. The study will be carried out in keeping with local legal requirements and international regulations.

7.1.1 Informed Consent of the Subject

Subjects who meet all inclusion criteria and none of the exclusion criteria are deemed eligible. Before being enrolled in the clinical study, the subject must provide a written consent form to participate in the study after the nature, scope and possible consequences of the clinical study have been explained both orally and in writing. Subjects should be aware that if they are enrolled/randomized to the study, they will be followed for the study whether or not they undergo invasive strategy as allocated. All subjects who signed informed consent form must be listed on the Screening Log.

7.1.2 Approval of the Study Protocol

Before the start of the study, the study protocol, the informed consent, and other appropriate documents must be submitted to and approved by the local Ethics Committee (EC) and the appropriate regulatory authorities in accordance with local legal requirements. Documentation of Ethics Committee approvals will be required before the site is activated to randomize.

7.2 Maintenance of Records

The Investigator agrees to obtain a correctly completed informed consent form for each subject included in the study. The investigator will maintain a personal list of subject numbers and subject names to enable records to be found at a later date. The Investigator must maintain all study records, subject files, and other source data for the maximum period of time permitted by the hospital, institution, private practice, national regulations, or Sponsor. For trials performed in the European

Community, the Investigator is required to arrange for the retention of the subject identification codes for at least 15 years after the completion or discontinuation of the trial.

7.3 Confidentiality

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data will be secured against unauthorized access.

The Investigator agrees to maintain the confidentiality of the study protocol.

7.4 Data Management

Data will be collected on electronic case report forms (CRFs). The CRF must be signed by the investigator or other appropriate individuals who are authorized by the investigator. The signing of the 'Study completion – Investigator's statement CRF' must be done by the investigator and is considered to be the final authorization of the CRFs.

7.5 Source Documentation

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office

charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The site will make available all source documents for inspection. The following information should be included in the subject's medical record:

- Subject's name and contact information
- The fact that the subject is participating in an approved clinical investigation
- The clinical investigation title and reference number
- The date the subject was enrolled into the trial and the subject ID number
- A statement that written informed consent was obtained
- Date of procedure and device lot number
- Dates of all visits
- Lists of medications
- Documentation of Adverse Events
- Date subject exited the clinical investigation, and a notation as to whether the subject completed the clinical investigation or discontinued, with the reason for early termination

7.6 Protocol Deviations

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. The investigator should not deviate from the protocol.

In some cases, failure to comply with the protocol may impact the integrity of the study data or be considered failure to protect the rights, safety, and well-being of subjects. These deviations are considered Major Deviations, and include:

- Failure to obtain informed consent
- Enrollment of a subject that did not meet the inclusion/exclusion criteria

The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the protocol. Relevant information for each deviation will be documented as soon as possible on the applicable eCRF. The site will submit the eCRF to the Sponsor.

The PI is required to adhere to local regulatory requirements for reporting deviations to EC.

An investigator shall notify the Sponsor and the reviewing EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an

emergency, prior approval by the Sponsor is required for changes in or deviations from the investigational plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and EC approval are also required.

8 DATA PROTECTION

All information related to the participation of a subject in this study will be treated with the utmost confidentiality, in accordance with good clinical practice (Decree of the Ministry of Health of 15 July 1997, and subsequent amendments and additions) and regulations on the protection of personal data: Information and Consent pursuant to Legislative Decree no. 196 of 30/06/2003 and the European General Data Protection Regulation (GDPR - General Data Protection Regulation), which came into force on 25 May 2018.

9 MONITORING

It is the responsibility of the Sponsor to ensure the clinical investigation is conducted, recorded and reported according to the approved protocol, subsequent amendment(s), applicable regulations and guidance documents. Monitoring of this study will be conducted according to the study-specific Monitoring Plan.

Prior to beginning the clinical investigation, the Sponsor will contact the investigator or designee to discuss the clinical investigation and data

requirements. A designated monitor will periodically review the subject records and associated source documents. The investigator shall make subject and clinical investigation records available to the clinical monitor for monitoring. The study monitor(s) will audit study records, CRFs, source documents, and other data relating to the study. The Investigator may redact such records, source documents, and other data to the extent reasonably necessary to protect subject confidentiality.

10 COMPLIANCE

10.1 Quality Assurance Audits and Regulatory Inspections

The investigator and/or delegate should contact the Sponsor immediately upon notification of a regulatory authority inspection at the site. A monitor or designee will assist the investigator and/or delegate in preparing for the audit. The Sponsor may perform quality assurance audits, as required.

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

10.2 Repeated and Serious Non-Compliance

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

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

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

11 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

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

A Principal Investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigational sites for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation or when so instructed by the EC or regulatory authority, the Sponsor may suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigators, EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the EC or regulatory authority, where appropriate, will be obtained before the clinical investigation resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual investigational site in the interest of safety, the Sponsor will inform all other Principal Investigators.

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

12 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

13 PUBLICATION POLICY

Publication planning and authorship determinations will be overseen by the Sponsor, and investigators will be notified via email about the dissemination of study data and opportunities for involvement as authors on publications/presentations.

14 REFERENCES

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3. Zampieri P, Colombo A, Almagor Y, Maiello L, Finci L. Results of coronary stenting of ostial lesions. Am J Cardiol. 1994;73:901-903.

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7. Chetcuti SJ, Moscucci M. Double-wire technique for access into a protruding aorto-ostial stent for treatment of in-stent restenosis. Catheter Cardiovasc Interv. 2004;62:214-217.
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9. Rajaraman P, Doody MM, Yu CL, et al. Journal Club: Cancer risks in U.S. radiologic technologists working with fluoroscopically guided interventional procedures 1994-2008. AJR Am J Roentgenol 2016;206:1101-9.