Clinical Study Protocol

A Study to EXhibit Percutaneous coronary Artery dilatation with Non-Slip Element balloon

(EXPANSE-PTCA)

Study Protocol Number: RDX-CL-5000

Revision: B, 03Dec2021

ClinicalTrials.gov Identifier: NCT04985773

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Signature: 

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Signature: 

Date: 12/3/2021

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Scott Brown, PhD, Chief Scientific Strategist, BRIGHT Research Partners

Principal Investigator Signature

I have read the clinical study protocol and agree to adhere to the requirements of this protocol in accordance with the ICH guidelines for good clinical practices, ISO 14155, and applicable FDA regulations.

Printed Name: _____ **Site #:** _____

Signature: _____ **Date:** _____

infraredx™ A NIPRO COMPANY	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Infraredx Study Number: RDX-CL-5000**
Study Title	A Study to EXhibit Percutaneous coronary Artery dilatation with Non-Slip Element balloon (EXPANSE-PTCA)
Identifying Regulatory Numbers	FDA IDE number – G210195 Clinicaltrials.gov – NCT 04985773
Study Objective	To evaluate safety and effectiveness of the Lacrosse NSE ALPHA coronary dilatation catheter during percutaneous coronary intervention in subjects with stenotic coronary arteries.
Device Description	The Lacrosse NSE ALPHA is a rapid exchange percutaneous transluminal coronary angioplasty balloon catheter with non-slip element nylon threads that focus dilatation force to reduce balloon slippage during inflation. The three nylon threads are 0.39 mm in height, located at 120° intervals parallel to the shaft, and bonded at the distal and proximal ends of the 13 mm long semi-compliant balloon. Inside the balloon, two radiopaque markers indicate the working length of the balloon to guide proper positioning in the targeted lesion. A hydrophilic coating is applied to the catheter shaft and tapered distal tip. The proximal shaft contains catheter insertion depth markers at 93 cm and 103 cm, and the proximal hub enables balloon inflation and deflation using a standard inflation device. The 2.7 Fr catheter is compatible with 0.014” guidewires and the 13 mm long semi-compliant balloon is available in eight diameters ranging from 2.0 mm to 4.0 mm. *Note: The Lacrosse NSE ALPHA is approved for marketing in 28 countries and the European Union.*
Proposed Device Indications for Use	The Lacrosse NSE ALPHA coronary dilatation catheter is indicated for balloon dilatation of the stenotic portion of the coronary artery including both *de novo* and in-stent restenosis, for the purpose of improving myocardial perfusion. This device is also indicated for the post-delivery expansion of balloon expandable stents.
Study Design	Prospective, multi-center, single arm clinical study. Subjects will be followed through hospital discharge.
Number of Sites & Subjects	200 subjects will be treated at up to 15 investigational sites in the U.S., including a minimum of 30 subjects with in-stent restenosis. Enrollment will continue until both the overall target of 200 and the ISR cohort of 30 have been obtained. No single site will enroll more than 20% of the total enrollment.
Study Population	Patients with stenotic coronary artery disease.
Primary Endpoint	Device procedural success, defined as: • Successful delivery, inflation, deflation, and withdrawal of the study balloon; and • No evidence of device-related vessel perforation, flow limiting dissection (grade C or higher per Clinical Events Committee (CEC) adjudication) or reduction in thrombolysis in myocardial infarction (TIMI) flow from baseline (per core laboratory assessment); and • Final TIMI flow grade of 3 at the conclusion of the PCI procedure per core laboratory assessment.

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	This endpoint will be presented as the proportion of subjects experiencing device procedural success. The proportion of target lesions meeting the primary endpoint will be concurrently calculated and presented as a secondary endpoint, as noted below
Secondary Endpoints	1. Angiographic procedural success, defined as final diameter stenosis ≤50% in at least one of the Lacrosse NSE ALPHA attempted lesions following completion of the interventional procedure, including adjunctive stenting per core laboratory assessment. 2. Major adverse cardiac events (MACE) through hospital discharge per CEC adjudication. MACE is defined as a composite of: • All-cause death • Myocardial infarction • Clinically indicated target lesion revascularization 3. Stent thrombosis within the target vessel(s) through hospital discharge using ARC-2 definitions for definite & probable, per CEC adjudication. 4. Clinically significant arrhythmia (defined as those requiring intervention) through hospital discharge, per CEC adjudication. 5. Occurrence of Lacrosse NSE ALPHA balloon rupture, per device deficiency eCRF. 6. Change in minimum lumen diameter following use of Lacrosse NSE ALPHA catheter, measured by quantitative coronary angiography per core laboratory assessment. 7. Device procedural success defined as for the primary endpoint, calculated and presented per target lesion. Secondary endpoints 1 through 5 are defined at a subject level and will be presented as the proportion of subjects experiencing the above events. In cases where multiple events per subject may be observed (e.g., adverse events), the primary analysis will be at the subject level but total event counts will also be reported. Secondary endpoints 6 and 7 are defined at the lesion level and statistical analyses of these endpoints will account for within-subject correlation as some subjects will have more than one target lesion, using generalized estimating equations with an exchangeable correlation structure.
Study Eligibility Criteria	**Subjects must meet all the following <u>inclusion</u> criteria:** <u>General inclusion criteria</u> 1. Age 18 years or older. 2. Willing to provide written informed consent and written HIPAA authorization prior to initiation of study-related procedures. 3. Agree to not participate in any other clinical study, during hospitalization for the index procedure that would interfere with the endpoints of this study. 4. Clinical evidence of ischemic heart disease, stable/unstable angina, or silent ischemia. 5. Acceptable candidate for PCI and emergency coronary artery bypass grafting and is planned for possible PTCA and/or stent placement.

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Angiographic inclusion criteria

6. *De novo* or restenotic lesion(s) in native coronary arteries, including in-stent restenosis.
7. A maximum of two lesions, including at least one target lesion, in single or double vessel coronary artery disease.
    a) If two target lesions are defined, then no non-target lesions can be treated.
    b) If a single target lesion is defined, then a single non-target lesion may be treated, but if so, it must be located in a different coronary artery from the target lesion.
8. Target lesion(s) must have a reference vessel diameter between 2.0 mm and 4.0 mm by visual estimation.
9. Target lesion(s) must have a diameter stenosis of (a) ≥70% by visual estimation or (b) >50% by visual estimation and a fractional flow reserve (FFR) of <0.80 or resting full-cycle ratio (RFR) or instantaneous wave-free ratio (iFR) <0.9.
10. Treatment of non-target lesion, if any, must be completed prior to treatment of target lesion; must not, in the opinion of the investigator, impact the conduct or completion of the index procedure; and must be deemed a clinical angiographic success as visually assessed by the investigator.

Subjects must not meet any of the following exclusion criteria:

General exclusion criteria

1. Known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, anti-platelet medications, a clopidogrel non-responder, or sensitivity to contrast media that cannot be adequately pre-medicated or replaced with a clinically suitable alternative.
2. Known diagnosis of type I myocardial infarction (resulting from primary reduction of flow from a culprit lesion likely to have a thrombotic component) within 7 days prior to the index procedure.
3. Known pregnancy or is nursing. Women of child-bearing potential should have a documented negative pregnancy test within 7 days prior to index procedure.
4. Planned target lesion treatment with atherectomy (rotational, orbital or laser), cutting balloon, thrombectomy, lithotripsy or an unapproved device during the index procedure.
5. Serum creatinine >2.0 mg/dl within 7 days prior to the index procedure.
6. Cerebrovascular accident within 6 months prior to the index procedure.
7. Active peptic ulcer or active gastrointestinal bleeding within 6 months prior to the index procedure.
8. Left ventricular ejection fraction <30% based on most recent measurement within a year of the index procedure (if LVEF is not available in the medical records, it may be obtained at the time of the index procedure, prior to enrollment).
9. Target lesion located within a bypass graft (venous or arterial) or graft

infraredx™ A NIPRO COMPANY	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Infraredx Study Number: RDX-CL-5000**
	anastomosis. 10. Previous percutaneous intervention, within 9 months before the study procedure, on lesions in a target vessel (including side branches) that are located within 10 mm from the current target lesion. 11. Target lesion(s) with complete total occlusion (CTO) defined as the complete obstruction of a native coronary artery, exhibiting TIMI 0 or TIMI 1 flow, with an occlusion duration of at least 3 months. 12. Unstable hemodynamics or shock. 13. Other medical condition which might, in the opinion of the investigator, put the patient at risk or confound the results of the study. <u>Angiographic exclusion criteria</u> 14. Target lesion(s) longer than 32 mm by visual estimation. 15. Extreme angulation (90º or greater) within 5 mm of the target lesion. 16. Target lesion(s) demonstrating flow limiting dissection (NHLBI Grade C or higher) prior to deployment of the Lacrosse NSE ALPHA. 17. Unprotected left main coronary artery disease (>50% diameter stenosis). 18. Coronary artery spasm of the target vessel in the absence of a significant stenosis. 19. Target lesion(s) with angiographic presence of probable or definite thrombus. 20. Target lesion(s) involves a bifurcation requiring treatment with more than one stent or pre-dilatation of a side branch >2.0 mm in diameter. 21. Target lesion(s) located in bifurcation beyond stent struts. 22. Target lesion(s) located distal to an implanted stent. 23. Target lesion(s) with stent damage. 24. Non-target lesion that meets any of the following criteria: • Located within a bypass graft (venous or arterial) • Located in an unprotected left main coronary artery • A CTO • Involves a bifurcation
Study Duration	Enrollment is expected to take approximately 12 months. Each study subject will actively participate in the study through hospital discharge. The overall study duration, from subject enrollment through final report, is expected to be approximately 18-24 months.
Study Sponsor	Infraredx, Inc. 28 Crosby Drive, Suite 100 Bedford, MA 01730 Telephone: 781-221-0053
National Principal Investigator	Mitchell Krucoff, MD Professor of Medicine Duke University School of Medicine

infraredx™ A NIPRO COMPANY	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Infraredx Study Number: RDX-CL-5000**
Contract Research Organization	BRIGHT Research Partners (www.brightresearchpartners.com) 730 2nd Avenue South, Suite 500 Minneapolis, MN 55402 Telephone: 612-345-4544 (general office line)
Core Lab	Alexandra Lansky MD, FACC, FAHA, FSCAI, FESC Angiographic Core Laboratory Yale Cardiovascular Research Group

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1.0 ABBREVIATIONS

The following is a list of abbreviations used in the body of this document. Abbreviations solely used in tables (e.g., table headers) are described in the table footer and are not included below.

Abbreviation	Description
BMS	bare metal stent
CABG	coronary artery bypass grafting
CEC	Clinical Events Committee
CFR	Code of Federal Regulations (U.S.)
CRF/eCRF	case report form / electronic case report form
CRO	clinical research organization
CTO	chronic total occlusion
DES	drug-eluting stent
EDC	electronic data capture (database)
FDA	Food and Drug Administration (U.S.)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IFU	instructions for use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	in-stent restenosis
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
MI	myocardial infarction
MLD	minimum lumen diameter
NHLBI	National Heart, Lung, and Blood Institute
NSE	non-slip element
NSTEMI	Non-ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
PI	principal investigator
PG	performance goal
PTCA	percutaneous transluminal coronary angioplasty
QCA	quantitative coronary angiography
RVD	reference vessel diameter

Abbreviation	Description
RX	rapid exchange
SAE	serious adverse event
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
TIMI	thrombolysis in myocardial infarction
TLR	target lesion revascularization
UADE	unanticipated (serious) adverse device effect

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2.0 CLINICAL BACKGROUND

Percutaneous coronary intervention (PCI) has evolved over the past 20 years from simple balloon angioplasty for treating atherosclerotic plaques in arteries to more progressive treatments, such as coronary stents, laser therapy, and radiation therapy. Two treatments remain in the forefront of interventional cardiology: percutaneous transluminal coronary angioplasty (PTCA) and coronary stenting. PTCA is a therapeutic technique to dilate occlusive lesions of the coronary artery. Application of this technique requires tools including PTCA balloon catheters, guiding catheters, guidewires, balloon inflation devices, and catheter introducers, as well as equipment such as cineradiographic X-ray machines, also referred to as fluoroscopy.

A PTCA balloon may be used in patients with acute myocardial infarction to treat calcified lesions, restenotic lesions, and intra-stent stenosis, and to perform predilatation for drug-eluting stents (DES) and bare metal stents (BMS). While BMS treatment dramatically reduces the incidence of dissection, elastic recoil, and remodeling, the concern of interest becomes in-stent restenosis (ISR), often leading to revascularization. DES therapy has subsequently led to a substantial reduction in the incidence of ISR, but ISR nevertheless remains among the consequential potential sequelae (Singh).

Heavily calcified lesions – markers of advanced atherosclerosis that are correlated with multivessel coronary disease and complex lesions – present a challenge for PTCA and stenting procedures due to their “higher risk of immediate complications, late failure due to stent under expansion and malapposition, and consequently poor clinical outcome” (Dini). According to Dini, the prevalence of moderate and severe calcific coronary stenoses ranges between 18% and 26%, and these lesions “are a predictor of a worse clinical outcome, associated with higher mortality, major adverse cardiovascular events (MACE) and target vessel failure on multivariate analysis after correction for confounders” (Dini).

With traditional semi-compliant PTCA balloon catheters, calcified lesions can cause the balloon to form a dog-bone shape, creating excessive pressures at the balloon edges that can cause coronary dissections or perforations (Dini). One method to avoid this dog-bone effect is the use of non-compliant balloons, which allow for higher inflation pressures and provide higher forces in a focal segment of the target lesion. Traditional non-compliant balloon catheters do not, however, contain mechanisms to prevent slippage of the balloon. Such slippage (frequently termed “watermelon seeding”) can have damaging effect on the artery and consequently lead to undesirable outcomes (Singh).

Cutting balloons, such as the Flextome Cutting Balloon introduced by Boston Scientific in 1991, provided another innovation aimed at addressing the challenges in treating calcified coronary lesions. These devices contain longitudinal microblades on the surface of the balloon that cut the inner surface of the vessel, reducing recoil, minimizing neointima proliferation, and reducing balloon slippage. Due to high crossing profiles and unfavorable clinical results, including a significantly higher perforation rate, the European Society of Cardiology and American College

of Cardiology guidelines have discouraged the use of cutting balloons, with the exception of restricted applications for resistant lesions (Dini).

Scoring balloons, with their semi-compliant balloons encircled by scoring elements, are smaller profile devices than cutting balloons, and because they can be fully expanded with a low inflation pressure, Dini notes that they produce “less trauma to vessel walls and a minor risk of coronary dissections” (Dini).

Several scoring balloon catheters have been commercially available to treat mild to moderate calcified lesions, including the AngioSculpt (Spectranetics-Philips), Flextome and Wolverine (Boston Scientific), Chocolate (QT Vascular/Medtronic/Teleflex), Fx miniRAIL (Guidant, no longer manufactured), and Scoreflex (OrbusNeich Medical).

The Lacrosse NSE ALPHA coronary dilatation catheter, which has been available in markets outside the U.S. since 2013, is a rapid exchange (RX) semi-compliant balloon catheter with nylon thread elements designed to limit the occurrence of balloon slippage. This study is intended to evaluate safety and effectiveness of the Lacrosse NSE ALPHA during PCI in subjects with stenotic coronary arteries.

3.0 TREATMENT DESCRIPTION

3.1 Device Description

The Lacrosse NSE ALPHA coronary dilatation catheter is a rapid exchange (RX) PTCA balloon catheter with non-slip element (NSE) nylon threads that focus dilatation force to reduce balloon slippage during inflation (**Figure 1**). The three nylon threads are 0.39 mm in height, located at 120° intervals parallel to the shaft, and bonded at the distal and proximal ends of the 13 mm long semi-compliant balloon (**Figure 2**). Inside the balloon, two radiopaque markers indicate the working length of the balloon to guide proper positioning in the target lesion.

The distal section of the 2.7 Fr catheter comprises a dual-lumen shaft; the outer lumen is for balloon dilatation, and the inner lumen allows for rapid exchange of 0.014” or smaller guidewires. A hydrophilic coating is applied to the catheter shaft and tapered distal tip. The proximal shaft contains catheter insertion depth markers at 93 cm and 103 cm, and the proximal hub enables balloon inflation and deflation using a standard balloon inflation device.

The device is available in eight balloon diameters ranging from 2.0 mm to 4.0 mm (**Table 1**). The nominal inflation pressure is 6 atm and the rated burst pressure is 14 atm. A balloon compliance chart is provided in the device instructions for use (IFU). The device is packaged sterile with a balloon protective tube and stylet that are removed prior to use.

Figure 1: Lacrosse NSE ALPHA

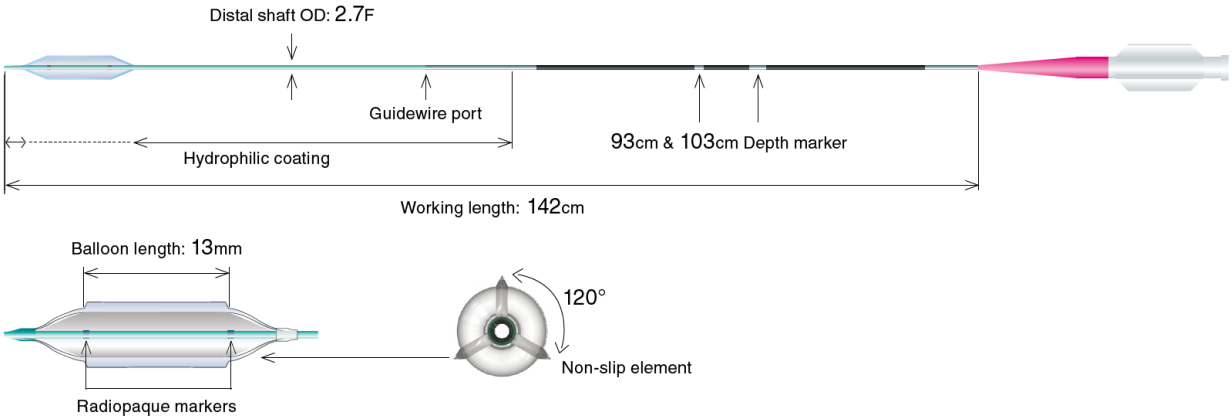

Figure 2: Non-Slip Element (NSE) Nylon Threads

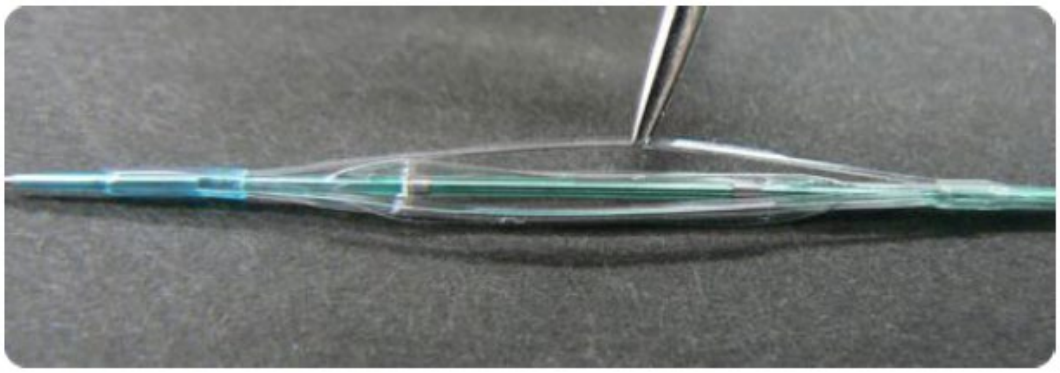

Table 1: Lacrosse NSE ALPHA Model Numbers

Model #	Balloon size
NSA20013	2.00 mm x 13 mm
NSA22513	2.25 mm x 13 mm
NSA25013	2.50 mm x 13 mm
NSA27513	2.75 mm x 13 mm
NSA30013	3.00 mm x 13 mm
NSA32513	3.25 mm x 13 mm
NSA35013	3.50 mm x 13 mm
NSA40013	4.00 mm x 13 mm

3.1.1 Device Manufacturer

The study sponsor and initial importer of the Lacrosse NSE ALPHA is Infraredx, Inc. (Bedford, MA). The device is manufactured by Goodman Co., Ltd. (Nagoya, Japan).

The Lacrosse NSE ALPHA is approved for marketing in 28 countries and the European Union.

3.1.2 Device Labeling / Instructions for Use

The IFU will be provided with each investigational device.

3.2 Principle of Operation / Mechanism

The Lacrosse NSE ALPHA is prepared and used similarly to standard commercially available PTCA balloon catheters. The catheter is guided over a 0.014" guidewire to the target lesion, and the balloon is inflated and deflated using a standard balloon inflation device filled with contrast media. The nylon NSE elements that are located over the balloon have a scoring effect that focuses dilatation force to reduce balloon slippage during inflation.

3.3 Proposed Indications for Use

The Lacrosse NSE ALPHA coronary dilatation catheter is indicated for balloon dilatation of the stenotic portion of the coronary artery including both *de novo* and in-stent restenosis, for the purpose of improving myocardial perfusion. This device is also indicated for the post-delivery expansion of balloon expandable stents.

4.0 OBJECTIVE

The objective of this study is to evaluate safety and effectiveness of the Lacrosse NSE ALPHA coronary dilatation catheter during PCI in subjects with stenotic coronary arteries.

5.0 ENDPOINTS

Endpoints selected for this trial, including the primary endpoint, are common measures of safety and effectiveness for comparable devices in the population under study; in particular, the primary endpoint is identical or nearly identical to recent/ongoing regulatory studies of the Scoreflex NC, Sapphire II PRO, Emerge, Mini Trek RX, and Sprinter Legend balloon catheters.

5.1 Primary Endpoint

The primary endpoint for the study is device procedural success, defined as:

- Successful delivery, inflation, deflation, and withdrawal of the study balloon; and
- No evidence of device-related vessel perforation, flow limiting dissection (grade C or higher, per Clinical Events Committee (CEC) adjudication) or reduction in thrombolysis in myocardial infarction (TIMI) flow from baseline (per core laboratory assessment); and
- Final TIMI flow grade of 3 at the conclusion of the PCI procedure per core laboratory assessment.

This endpoint will be presented as the proportion of subjects experiencing device procedural success. The proportion of target lesions meeting the primary endpoint will be concurrently calculated and presented as a secondary endpoint, as noted below.

5.2 Secondary Endpoints

The secondary endpoints for the study are:

1. Angiographic procedural success, defined as final diameter stenosis ≤50% in at least one of the Lacrosse NSE ALPHA attempted lesions following completion of the interventional procedure, including adjunctive stenting per core laboratory assessment.
2. MACE through hospital discharge per CEC adjudication. MACE is defined as a composite of:
   - All-cause death
   - Myocardial infarction (MI)
   - Clinically indicated target lesion revascularization (TLR)
3. Stent thrombosis (ST) within the target vessel(s) through hospital discharge using ARC-2 definitions for definite & probable, per CEC adjudication.
4. Clinically significant arrhythmia (defined as those requiring intervention) through hospital discharge, per CEC adjudication.
5. Occurrence of Lacrosse NSE ALPHA balloon rupture, per device deficiency eCRF.
6. Change in minimum lumen diameter (MLD) following use of the Lacrosse NSE ALPHA catheter, measured by quantitative coronary angiography (QCA) per core laboratory assessment.
7. Device procedural success defined as for the primary endpoint, calculated and presented per target lesion.

Secondary endpoints 1 through 5 are defined at a subject level and will be presented as the proportion of subjects experiencing the above events. In cases where multiple events per subject may be observed (e.g., adverse events), the primary analysis will be at the subject level but total event counts will also be reported. Secondary endpoints 6 and 7 are defined at the lesion level and statistical analyses of these endpoints will account for within-subject correlation as some subjects will have more than one target lesion, using generalized estimating equations with an exchangeable correlation structure.

5.3 Ancillary Data

Additional ancillary data to be collected and evaluated include:

- Balloon slippage
- Catheter performance questionnaire
- All adverse events, categorized per CEC adjudication
- Device deficiencies

- Protocol deviations
- Screen failure tracking

6.0 STUDY DESIGN

6.1 Overall Design

The investigation is a prospective, multi-center, single arm clinical study. Subjects will be followed through hospital discharge. The study design is similar to comparable devices in the population under study; in particular, the Scoreflex NC is currently being evaluated in an ongoing clinical study to support regulatory market applications.

After screening for initial inclusion and exclusion criteria, eligible subjects will be asked to participate in the study by signing a consent form. Following consent, subjects will undergo a baseline visit where additional eligibility criteria will be assessed. An angiogram will be completed to assess for angiographic eligibility. If any angiographic inclusion criteria are not met or any of the angiographic exclusion criteria are met, the patient will not be enrolled. If all angiographic inclusion criteria are met and none of the angiographic exclusion criteria are met, subjects may undergo treatment with the Lacrosse NSE ALPHA. If a non-target lesion is identified, it must be treated successfully prior to target lesion treatment. Once treatment of the target lesion(s) has been attempted, the subject will be considered enrolled in the study.

Subjects will be followed through hospital discharge.

6.2 Number of Sites & Subjects

The study will be conducted in up to 15 investigational sites in the U.S. This study will enroll and treat 200 subjects, including a minimum of 30 subjects with ISR. Enrollment will continue until both the overall target of 200 and the ISR cohort of 30 have been obtained. More specifically, enrollment of non-ISR subjects will be capped at 170 such that if and when this maximum has been achieved without 30 ISR subjects, only ISR subjects will be permitted to be enrolled until the minimum of 30 has been reached, for a total of 200 subjects. Detailed sample size calculations and statistical methods are contained in **Section 8.6** and in the statistical analysis plan. No single site will enroll more than 20% of the total enrollment.

6.3 Study Population

The population for this study is subjects with stenotic coronary artery disease who are suitable candidates for PTCA.

The study will be conducted in adult subjects (18 years or older) and does not include any age, gender, or racial and ethnic origin restrictions. Women who have known pregnancy or who are nursing are excluded because of the risks of radiation exposure that occurs during the PTCA procedure and the medications (e.g., blood thinners) that may be needed.

Medicare-eligible patients (age 65 and up) will be included in the subject population. Two recent articles support that a large number of subjects undergoing PCI are in this age group.

- A publication (Kandzari) from the Scoreflex NC trial (IDE G180168, NCT NCT03763747) reported mean age of 67.3 [SD 8.98] years. The product and intended patient population in the Scoreflex NC trial are substantially similar to those in the EXPANSE-PTCA study; these data indicate that a considerable fraction – likely a majority -- of subjects in the current study population will be Medicare-eligible.
- A retrospective cohort study (Alkhouli) used a national inpatient claims-based database to identify patients undergoing PCI or CABG from 2003 to 2016 and reported demographic characteristics into 3 distinct time frames (2003-2007, 2008-2012, and 2013-2016). Of the 1,877,560 patients that underwent PCI in the most recent time frame (2013-2016), 43.1% were aged 65-85, with an additional 4.8% were greater than 85 years. In the same cohort, 60.9% of patients were Medicare or Medicaid patients.

Based on these two publications, and the intended population for this study, study enrollment is anticipated to include a substantial proportion of Medicare-eligible subjects and results are therefore expected to be generalizable for Medicare beneficiaries due to age, disability, or other eligibility status.

6.4 Study Duration

Enrollment is expected to take approximately 12 months. Each subject will actively participate in the study through hospital discharge. The overall study duration, from subject enrollment through final report, is expected to be approximately 18 – 24 months.

6.5 Subject Eligibility Criteria

6.5.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria:

General inclusion criteria

1. Age 18 years or older.
2. Willing to provide written informed consent and written Health Insurance Portability and Accountability Act (HIPAA) authorization prior to initiation of study-related procedures.
3. Agree to not participate in any other clinical study, during hospitalization for the index procedure, that would interfere with the endpoints of this study.
4. Clinical evidence of ischemic heart disease, stable/unstable angina, or silent ischemia.
5. Acceptable candidate for PCI and emergency coronary artery bypass grafting (CABG) and is planned for possible PTCA and/or stent placement.

Angiographic inclusion criteria

6. *De novo* or restenotic lesion(s) in native coronary arteries, including in-stent restenosis.
7. A maximum of two lesions, including at least one target lesion, in single or double vessel coronary artery disease.
    a. If two target lesions are defined, then no non-target lesions can be treated.

b. If a single target lesion is defined, then a single non-target lesion may be treated, but if so, it must be located in a different coronary artery from the target lesion.

8. Target lesion(s) must have a reference vessel diameter (RVD) between 2.0 mm and 4.0 mm by visual estimation.
9. Target lesion(s) must have a diameter stenosis of (a) ≥70% by visual estimation or (b) >50% by visual estimation and a fractional flow reserve (FFR) of <0.80 or resting full-cycle ratio (RFR) or instantaneous wave-free ratio (iFR) <0.9.
10. Treatment of non-target lesion, if any, must be completed prior to treatment of target lesion; must not, in the opinion of the investigator, impact the conduct or completion of the index procedure; and must be deemed a clinical angiographic success as visually assessed by the investigator.

6.5.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

General exclusion criteria

1. Known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, anti-platelet medications, a clopidogrel non-responder, or sensitivity to contrast media that cannot be adequately pre-medicated or replaced with a clinically suitable alternative.
2. Known diagnosis of type I myocardial infarction (resulting from primary reduction of flow from a culprit lesion likely to have a thrombotic component) within 7 days prior to the index procedure.
3. Known pregnancy or is nursing. Women of child-bearing potential should have a documented negative pregnancy test within 7 days prior to index procedure.
4. Planned target lesion treatment with atherectomy (rotational, orbital or laser), cutting balloon, thrombectomy, lithotripsy or an unapproved device during the index procedure.
5. Serum creatinine >2.0 mg/dl within 7 days prior to the index procedure.
6. Cerebrovascular accident within 6 months prior to the index procedure.
7. Active peptic ulcer or active gastrointestinal bleeding within 6 months prior to the index procedure.
8. Left ventricular ejection fraction (LVEF) <30% based on most recent measurement within a year of the index procedure (if LVEF is not available in the medical records, it may be obtained at the time of the index procedure, prior to enrollment).
9. Target lesion located within a bypass graft (venous or arterial) or graft anastomosis.
10. Previous percutaneous intervention, within 9 months before the study procedure, on lesions in a target vessel (including side branches) that are located within 10 mm from the current target lesion(s).
11. Target lesion(s) with complete total occlusion (CTO) defined as the complete obstruction of a native coronary artery, exhibiting TIMI 0 or TIMI 1 flow, with an occlusion duration of at least 3 months.

12. Unstable hemodynamics or shock.
13. Other medical condition which might, in the opinion of the investigator, put the patient at risk or confound the results of the study.

Angiographic exclusion criteria

14. Target lesion(s) longer than 32 mm by visual estimation.
15. Extreme angulation (90º or greater) within 5 mm of the target lesion.
16. Target lesion(s) demonstrating flow limiting dissection (NHLBI Grade C or higher)
17. Unprotected left main coronary artery disease (>50% diameter stenosis).
18. Coronary artery spasm of the target vessel in the absence of a significant stenosis.
19. Target lesion(s) with angiographic presence of probable or definite thrombus.
20. Target lesion(s) involves a bifurcation requiring treatment with more than one stent or pre-dilatation of a side branch >2.0 mm in diameter.
21. Target lesion(s) located in bifurcation beyond stent struts.
22. Target lesion(s) located distal to an implanted stent.
23. Target lesion(s) with stent damage.
24. Non-target lesion that meets any of the following criteria:
    - Located within a bypass graft (venous or arterial)
    - Located in an unprotected left main coronary artery
    - A CTO
    - Involves a bifurcation

7.0 STUDY METHODOLOGY

Study evaluations and data collection points are described below and visually represented in **Figure 3** and in **Table 2** below. To avoid missing data in the study, subjects should be followed for all regularly scheduled visits for safety and effectiveness assessments. Any reason for withdrawal from the study should be documented as described later in the protocol. See **Section 13.0** for definitions of adverse event and endpoint-related terms used in this section.

Study procedures should be followed carefully as they have been designed to address foreseeable factors that could compromise the outcome of the study or interpretation of results. This includes inclusion/exclusion criteria designed to address potential subject-related factors, treatment procedures to address foreseeable factors related to concomitant medication and/or medical procedures, and follow-up procedures to permit the demonstration of clinical performance and safety over a sufficient period of time.

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Figure 3: Study Flow Diagram

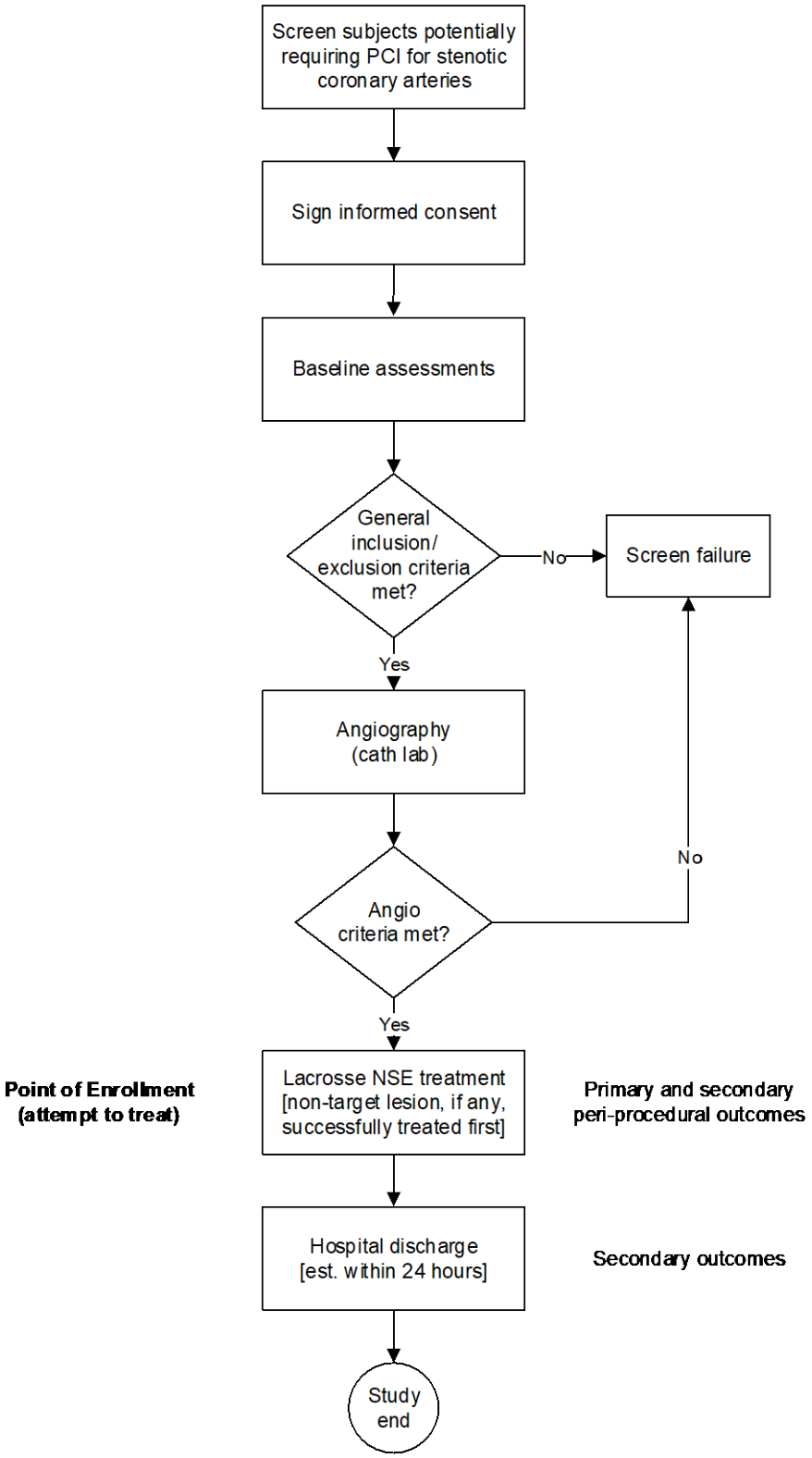

Table 2: Evaluations & Data Collection Points

Evaluations	Screening / Baseline	Treatment Procedure[1]	Post-Procedure/ Discharge
Subject informed consent	X		
Inclusion/exclusion assessment - general	X		
Demographics & medical/surgical history[2]	X		
Pregnancy test[3, 4]	X		
Serum creatinine[4]	X		
Coronary angiography (send to core lab)[5]		X	
Inclusion/exclusion assessment – angio[5]		X	
PCI procedure		X	
Device performance assessment		X	
Device deficiency assessment		X	
Adverse event assessment[6]		X	X
Catheter performance questionnaire			X

[1] Within 30 days of screening / baseline
[2] Medical history collected within 14 days of the index procedure
[3] If female with child-bearing potential
[4] Completed within 7 days of the index procedure
[5] Angiography occurs in cath lab, prior to treatment, to determine enrollment eligibility
[6] Adverse event assessment begins at the time of enrollment

7.1 Screening

Screening is defined as the process of reviewing a patient's medical records against the study eligibility criteria to determine if the patient is potentially eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria. Eligible patients are those potentially requiring PCI for stenotic coronary arteries.

If the investigator (or designee) determines the patient meets all clinical inclusion and exclusion criteria (except criteria verified by blood testing after consent), they can be consented for study participation, after which all remaining non-angiographic eligibility criteria will be verified prior to the procedure.

Final study eligibility can only be assessed in the cath lab using angiographic inclusion and exclusion assessments. During the pre-intervention angiography, some consented subjects may be determined ineligible for study enrollment; these subjects will be categorized as screen failures. Sites will be required to maintain a screen failure log, that contains rationale for subjects who became screen failures after consent.

7.2 Informed Consent Process

Prior to enrolling patients in this study, the site will be required to have an Institutional Review Board (IRB) approved informed consent form (ICF). The clinical research organization (CRO) must review any modifications made to the sponsor's template ICF prior to IRB submission.

Written informed consent will be obtained from the patient (or the patient's legal representative) prior to participation in the study. The investigator (or authorized designee) will explain the nature of the planned treatment and objectives of the study to the patient, along with any costs to the patient, payments for participation, and types of insurance provided (if applicable). The investigator will allow adequate time for the patient to read and review the consent form and to ask questions. When the investigator has reasonable assurance that the patient (or legal representative) has an acceptable level of comprehension and the patient (or legal representative) voluntarily agrees to participate, the patient (or legal representative) and the investigator (or authorized designee) will sign and date the IRB-approved ICF.

The site will retain the original signed ICF in the subject's study records and will provide a copy of the signed ICF to the subject. The site will document the consent process (e.g., that the subject was consented, the date on which the consent was obtained, and that a copy of the signed ICF was given to the subject) in the subject's medical records.

Subjects will be informed of any new information that may make him/her change their mind about staying in the study. Subjects may be asked to sign a new ICF if this occurs.

7.2.1 Vulnerable Population

The sponsor is not anticipating enrollment of a vulnerable patient population (ref. ISO 14155:2020 sections 5.7 and A.6.3).

7.2.2 Point of Enrollment & Numbering of Study Subjects

A patient will be considered enrolled as a study subject once an investigational Lacrosse NSE ALPHA catheter has entered the guiding catheter ("attempt to treat").

Note: Successful treatment of any non-target lesion is required prior to enrollment.

As soon as possible after a subject is enrolled, the site will notify the CRO, preferably by an entry in the electronic data capture (EDC) database or via email notification. The database will assign the lowest available patient enrollment ID, progressing sequentially for each enrolled subject (e.g., 0001, 0002, 0003). Subject ID assignment will follow Infraredx procedure CS0110.

7.3 Baseline

The following standard of care evaluations and assessments will be performed at baseline and documented on the relevant electronic case report forms (eCRFs):

- Demographics
- Medical and surgical history obtained within 14 days of the procedure (including key comorbidities and prior coronary interventions (e.g., PCI, CABG))

- Pregnancy test (if female with childbearing potential), per standard of care for PCI (within 7 days of procedure)
- Serum creatinine (within 7 days of procedure)

After the baseline evaluations, the inclusion and exclusion criteria should be re-reviewed to ensure that the subject continues to be eligible for the study.

7.4 Pre-PCI Procedure Angiogram

The site will follow standard catheterization procedures and angiographic procedures recommended by the core laboratory. A pre-procedure angiogram of the target lesion will be completed per the Angiographic Core Laboratory Guidelines prior to any interventions. Assessment of angiographic eligibility is based on a visual assessment of the pre-procedure angiogram by the investigator.

7.5 Treatment Procedure & Immediate Post-Procedure Assessment

The PCI procedure will be performed following these guidelines:

- A maximum of one non-target lesion, if identified, must be located in a different coronary artery from the target lesion and must be treated first and deemed a clinical angiographic success, as visually assessed by the physician. Study devices cannot be used on this non-target lesion.
- Target lesion will be treated using the Lacrosse NSE ALPHA following the device instructions for use.
- A target lesion composed of multiple focal lesions that can be covered with one stent will be considered as a single lesion.
- A separate Lacrosse NSE ALPHA study device must be used for treatment of each target lesion.

Additional procedures and interventions may be performed per standard of care at the discretion of the treating investigator (except those defined in the exclusion criteria).

Post-procedure angiographic imaging of the target lesion must be captured and performed per the instructions provided by the core laboratory and must be captured in the same precise manner as was used for the pre-procedure images. Angiographic images must be sent to the core lab following the instructions provided by the core laboratory.

Standard PCI procedural data will be collected on the eCRFs, such as:

- Vessel and lesion characteristics, including MLD and diameter stenosis (%)
- TIMI grade flow pre- and post-treatment
- Type and size of study devices used, including lot number
- Device performance assessment, including balloon slippage
- Procedural durations, including start/end times
- Air kerma (Gy) and total fluoroscopy time

- Adverse event assessment, including perforation and dissection classifications
- Device deficiency assessment

7.5.1 Post-procedure / Discharge

The following evaluations and assessments will be performed at 18-24 hours post-procedure or directly prior to discharge, whichever occurs first, and documented on the relevant eCRFs:

1. Catheter performance questionnaire
2. Adverse event assessment

After the subject is discharged, participation in the study is complete and the site will fill out the Study Completion eCRF. Subjects will continue to be followed by their physician per usual care.

7.6 Early Withdrawal / Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for several reasons including:

- Subject death
- Subject request for withdrawal (withdrawal of consent)
- Investigator decision, to be fully documented
- Adverse event

If a subject is discontinued from the study early, a Study Completion eCRF must be completed describing the reason for early discontinuation. If a subject chooses to withdraw from the study and also withdraws consent for disclosure of further information, no further evaluation(s) should be performed, and no additional data collected. The sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

8.0 STATISTICAL METHODS

8.1 Analysis Datasets

The primary analysis will consist of all available data on all subjects enrolled, referred to in ICH E9 (“Statistical Principles for Clinical Trials”) as the *full analysis set*. As the study is a treatment-only, single arm design, summaries of results will principally be presented for the entire study population.

8.2 General Principles

Continuous data will be summarized using descriptive statistics: mean, standard deviation, median, and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For endpoints analyzed at the subject level that can occur more than once in a single subject, such as adverse events, the percentage will be based on the number of subjects experiencing the event; both subject and event counts will be reported. For endpoints analyzed at the lesion level (secondary endpoints 6 and 7, as defined in **Section 5.2**), the lesion-level analysis will be considered primary.

All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

8.3 Analysis of Primary Endpoint

The primary endpoint will be presented as the proportion of subjects experiencing device procedural success.

These results will then be compared to a performance goal derived from studies of comparable products. As clinical evidence from FDA premarket approval (PMA) application submissions on similar products (e.g., AngioSculpt, Fx miniRAIL) involve a substantially different definition of the primary endpoint, the performance goal is based on recent studies in the LOX product code, as follows:

Device	N	Endpoint	Success rate
Sapphire II PRO	61	Successful use, no perf or grade C dissection, no reduction in TIMI, final TIMI 3	96.7% (59/61)
Emerge	60	Successful use, no perf or grade C dissection, no reduction in TIMI, final TIMI 3	98.3% (59/60)
Mini Trek Rx	71	Successful use, no clinically significant perf or grade C dissection, no clinically significant arrhythmias, no reduction in TIMI, final TIMI 3	98.5% (66/67[1])
		TOTAL	**97.9% (184/188)**

[1] Angiographic documentation associated with predilation with the study device was not available for 4 patients; accordingly, patient-level analysis related to the primary endpoint was performed for 67 patients.

The sample-size weighted rate of endpoint success in the above trials is then 97.9% as shown above.

Results are also available from the Scoreflex NC trial (Kandzari), which included a comparable primary endpoint and was achieved in 93.5% (187/200) of study subjects; as the product and intended patient population in the Scoreflex NC trial are substantially more similar to those in the present study than in the LOX studies cited above, it is prudent to account for these results.

To do so without overreliance on Scoreflex NC alone, we therefore adjust the tabulated outcomes from the LOX studies above by half of the difference compared to Scoreflex NC, or (97.9% - 93.5%) / 2 = 2.2%, to get a final value of 95.7%.

The studies cited above did not have statistical performance goals defined, while other trials with similar purposes and populations (e.g., AngioSculpt) used different endpoints; however, in general in the PCI space statistical margins such as 7% (e.g., FX miniRAIL), 9.4% (e.g., Asahi Intecc) and 10% (e.g., XIENCE) have been applied. Therefore, a value of 8%, within the typical range, will be applied.

With this statistical margin (i.e., delta), the performance goal is then 87.7%. Formally, the hypotheses to be tested for the primary endpoint are then as follows:

H0: $r \leq PG$

HA: $r > PG$,

where r is the proportion of endpoint successes and PG is the performance goal of 87.7% = 0.877.

The hypotheses will be tested at a one-sided alpha level of 0.05 and endpoint success will be declared if the performance goal is met (i.e., if the null hypothesis above is rejected in favor of the alternative hypothesis). For primary analysis, this endpoint will be tested on all subjects with available data, with a worst-case sensitivity analysis also incorporated as noted below.

Among the 200 subjects intended for enrollment, a subgroup of at least 30 is intended to be cases of in-stent restenosis. The value of 30 is a commonly used benchmark and is chosen to provide a reasonable sample size to characterize outcomes in this subgroup (Hogg, 2005), as well as a feasible target from a clinical perspective. The ISR subgroup is not intended for formal statistical hypothesis testing independent of the entire study cohort as the study is powered for the full 200 subjects planned for enrollment; hence no decision rule specific to ISR cases is defined. However, key outcomes, including the primary endpoint, will be compared between the *de novo* and ISR cohorts to assess any statistically significant differences. This testing will be performed on an exploratory basis and hence no alpha allocation for multiplicity is necessary, nor will overall analytical conclusions be driven by the number of ISR cases.

8.4 Analysis of Secondary Endpoints

Secondary endpoints 1 through 5 (as stated and numbered in **Section 5.2**) are defined at a subject level and will be presented as the proportion of subjects experiencing the above events. In cases where a subject-level analysis is specified but multiple events per subject may be observed (e.g., adverse events), the primary analysis will be at the subject level but total event counts will also be reported. Secondary endpoints 6 and 7 are defined at the lesion level and statistical analyses of this endpoint will account for within-subject correlation as some subjects will have more than one target lesion. For these endpoints, generalized estimating equations will be applied, using an exchangeable (within-subject) correlation structure.

Secondary endpoints defined as continuous measures (e.g., MLD) will be summarized according to the general principles in **Section 8.2**.

Secondary endpoints as defined in this protocol are not intended for labeling claims and hence no formal statistical hypotheses are defined *a priori.* Multiplicity of testing and associated alpha allocation (i.e., between the primary and secondary endpoints) is therefore not applicable to the current investigation.

8.5 Safety Analysis

Summary tables and listings will be provided for all reported adverse events, which will additionally be reported by seriousness and relatedness. Such summaries will comprise the

number and percentage of subjects with an adverse event and the total number of such events. The proportion of subjects with events will be considered primary for analysis of adverse events.

8.6 Sample Size

Based on the performance goal and hypothesis testing specified above, sample size and power were computed using SAS version 9.4 PROC POWER, assuming an exact test of a single binomial outcome against a performance goal (the null hypothesis). Postulating a primary endpoint success rate at the subject level of 93.5%, as observed in the Scoreflex NC trial, and with a null hypothesis of 87.7% per the performance goal constructed from the available literature, a sample size of 200 subjects provides 84% power to meet the endpoint using hypothesis testing as defined above. Under modest assumptions for missing data on study outcomes (e.g., 5% missingness), the power remains above 80%.

This sample size also reflects clinical trial practice in the space and in the study population of interest and matches the sample sizes from relevant regulatory studies including the Scoreflex NC and AngioSculpt primary clinical investigations.

8.7 Pooling of Data

As this investigation is a multi-center study, poolability of the primary endpoint will be assessed using Pearson's chi-square test, where sites enrolling fewer than 5 subjects will be dropped from the poolability analysis for sites, such that poolability findings will only be applied to sites with enrollment of at least 5 subjects. A resulting p-value less than 0.15 will be cause for investigation of potential causes of heterogeneity across clinical sites. Additionally, descriptive statistics for the primary endpoint will be tabulated and presented by site, including small (less than 5 subjects) sites.

8.8 Missing Data

All available data in the full analysis set will be used to evaluate study outcomes. Methods for replacing missing data, such as last value carried forward or multiple imputation, will not be employed for primary analyses; however, a sensitivity analysis of the primary endpoint incorporating worst-case assumptions (e.g., missingness equals failure) will be performed.

9.0 MEASURES TO AVOID & MINIMIZE BIAS

The study has several measures that have been implemented to avoid and minimize bias including:

- Use of an independent CRO for study operations management, monitoring, and data management
- Establishment of a CEC to independently review and adjudicate adverse events
- Use of an independent angiographic core laboratory for systematic review of images to remove potential for investigator bias

9.1 Clinical Events Committee

The Clinical Events Committee (CEC) which is made up of at least three non-investigator interventional cardiologists, will adjudicate adverse events and endpoints following written CEC adjudication guidelines. Sites will be expected to provide supporting de-identified source documentation as requested to assist with CEC adjudication.

9.2 Angiographic Core Laboratory

An angiographic core laboratory will be used to provide an unbiased assessment of angiographic imaging. The angiographic core laboratory will provide image acquisition and processing instructions to the sites. The angiographic core laboratory will follow its own charter or similar procedure to systematize their image review in compliance with the study protocol.

10.0 BENEFITS & RISK ANALYSIS

10.1 Potential Benefits of Study Participation

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with a study device may have the following benefits:

- Potentially lower-risk catheter-based revascularization of a coronary artery that may otherwise require surgical intervention via CABG
- Reduction in symptoms of coronary artery disease
- Improvement in quality of life

10.2 Alternative Treatment

There is no obligation for a patient to take part in this study. Alternative treatments may include:

- Surgical intervention via CABG
- Interventional procedure using other commercially available PTCA catheters

10.3 Potential Risks Associated with Study Participation

As with any surgical procedure, use of the study devices during PCI involves some risks. Risks associated with laboratory testing (i.e., blood draws) and the PCI procedure will be listed in the site's procedure consent form used per their standard of care. Potential risks associated with the Lacrosse NSE ALPHA may include but are not limited to:

- Air embolization
- Arrhythmia (including ventricular fibrillation, bradycardia, tachycardia)
- Arterial damage
- Arterial dissection
- Arterial or bypass graft occlusion
- Arterial perforation

- Arterial spasm
- Arteriovenous fistula
- Blood loss from puncture site
- Death
- Distal embolization
- Hematoma
- Hemorrhagic complications
- Hypertension
- Hypotension
- Infection
- Ischemia caused by long duration inflation
- Myocardial infarction
- Nausea or vomiting
- Palpitation
- Reaction (e.g., medicinal reaction or allergic reaction to contrast media)
- Restenosis following angioplasty
- Stroke
- Thrombosis
- Unstable angina

The frequency and severity of adverse events can vary, and may necessitate additional medical intervention, including surgery.

10.4 Methods to Minimize Risks

The Lacrosse NSE ALPHA was subjected to a risk analysis as part of the design control process. Results of pre-clinical bench and laboratory testing have demonstrated that the device is likely to be safe and perform as intended in clinical use. Additional Lacrosse NSE ALPHA laboratory and clinical experience is summarized in the Investigator Brochure. In addition, this device has been marketed outside the U.S. and experienced real-world clinical use since 2013.

To mitigate the risks described above, Infraredx and the CRO will work with interventional cardiologists trained in PTCA techniques, train all study personnel, and provide device labeling that contains all appropriate information to treat the patient. Risks will be further minimized through careful subject screening and selection, adherence to the scheduled assessments, and regular monitoring visits.

10.5 Benefit-to-Risk Rationale

The results from the risk analysis and risk mitigation measures, combined with extensive experience with the study device in commercial markets outside the U.S., support reasonable

assurance of the safety and efficacy of the Lacrosse NSE ALPHA, when used in a manner consistent with its labeling and intended use. The evidence supporting the safety and effectiveness of the study device is based on a foundation of market experience outside the U.S. since 2013, with the device now available in 28 countries plus the European Union. More than 340,000 units have been sold worldwide to date; these marketed devices all function similar to other market-released scoring balloon products, such as AngioSculpt (Spectranetics-Philips), Flextome and Wolverine (Boston Scientific), Chocolate (QT Vascular / Medtronic / Teleflex), and Fx miniRAIL (Guidant, no longer manufactured). In addition, the similarly functioning Scoreflex NC (OrbusNeich Medical) is currently under investigation. The evidence supports a clinical benefit-to-risk determination that is favorable for the Lacrosse NSE ALPHA.

11.0 ADVERSE EVENTS

11.1 Adverse Event Definitions

Adverse events will be assessed for seriousness and for relatedness to the investigational device and study procedure. Refer to **Section 13.1** for adverse event definitions.

11.2 Adverse Event Collection & Documentation

Collection of adverse events will start when subjects are enrolled and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the relatedness and outcome of the adverse event and to assess whether it meets the criteria for classification as an unanticipated adverse device effect (UADE) requiring immediate notification. All adverse events will be followed until resolution or investigator determination that the subject's condition is stable.

All reported adverse events will be documented on the Adverse Event eCRF. Copies of de-identified source documentation that contain significant information related to the event, such as progress notes, consultations, nurse's notes, operative reports and subject summaries may be requested by the sponsor, CRO, CEC, and/or angiographic core lab as needed for evaluation and adjudication.

The following are <u>not</u> considered adverse events for this study:

- Any condition that is recorded as pre-existing on the Baseline eCRF, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
- Any normal expected symptoms associated with PCI unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. The following are examples of the normal responses to all PCI procedures and are not considered adverse events:
    - Transient arterial spasm resolving spontaneously OR with medication only

- Transient sinus bradycardia with heart rate ≤50 bpm, with no hemodynamic impact, and resolving spontaneously (prophylactic placement and automatic activation of a cardiac pacer during this transient period does not constitute an intervention)
- Minor discomfort or bruise at the arterial access place
- Small amount of bleeding at point of arterial access that does not result in a hematoma >5 cm, need for transfusion, or hemodynamic compromise
- Side effects of standard-of-care medications

Device deficiencies will also be collected and reported on a Device Deficiency eCRF. If a device deficiency results in the subject experiencing any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, these outcomes will be reported as an adverse event on an Adverse Event eCRF. Any malfunctioning devices will be returned to the sponsor by the site for further evaluation.

In case of subject death, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the CRO. Any other source documents related to the death should also be provided to the CRO. If no source documents are available, the principal investigator (PI) is required to describe the circumstances of the subject's death in written communication (e.g., letter, e-mail).

11.3 Adverse Event Reporting Timeframes

The investigator is responsible for reporting serious adverse events to the IRB in accordance with the IRB's procedures. Unanticipated adverse device effects (UADEs) have special reporting requirements for both the investigator and sponsor, as described in 21 CFR 812.150:

- **Investigator Report:** If a subject experiences a UADE, the investigator must notify the sponsor and the reviewing IRB as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
- **Sponsor Report:** UADEs will be reported to the Food and Drug Administration (FDA), all reviewing IRBs, and participating investigators as soon as possible, but no later than 10 working days after receiving notice of the UADE.

11.4 Adverse Event Relatedness

The investigator and the CEC will assess the relatedness of adverse events to the investigational device and the study procedure using the categories listed below (see **Section 13.1** for definitions):

- Definitely
- Probably
- Possibly
- Unlikely
- Not Related

12.0 ADMINISTRATIVE PROCEDURES

12.1 Records & Reports

12.1.1 Case Report Forms

Worksheets may be used to collect subject data that is not readily available from the source documentation. An EDC database will be used to collect study-required data on eCRFs. The PI is responsible for ensuring the eCRFs are accurate and completed in a reasonable timeframe. The PI is required to review and approve the eCRF on the appropriate page(s) to verify the completeness, accuracy, and authenticity of the recorded data.

12.1.2 Sponsor / CRO Study Records

The sponsor and CRO are responsible for maintaining study records and reports per applicable ICH Good Clinical Practices (GCP), FDA regulations, ISO 14155, and applicable standard operating procedures and study specific-plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, and Statistical Analysis Plan).

Results on all pre-specified study outcomes will be released in interim reports, as needed, and in a final clinical study report that will be released within 6 months after study termination or completion. The release of this information, including negative outcomes, may be hastened if the study is terminated early.

12.1.3 Investigator Study Records

The investigator will securely maintain the following accurate, complete, and current records relating to their participation in the study as follows:

- All essential correspondence that pertains to the investigation.
- Records of each subject's case history and exposure to the investigational device. Case histories include the eCRFs and supporting data including, for example, signed and dated ICFs and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records will include:
    - Documents evidencing the informed consent process. The case history of each individual will document that informed consent was obtained at the appropriate time.
    - All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates and reasons for each deviation from the protocol.
- Signed investigator agreements, financial disclosure agreements, investigator signature pages, and curriculum vitae.

- IRB approval documents including approval of the protocol, protocol amendments, and the ICF.

12.1.4 Investigator Reporting Requirements

Investigator reporting requirements are noted in **Table 3** below.

Table 3: Investigator Reporting Requirements

Report	Submitted to	Description
Unanticipated adverse device effects (UADE)	Sponsor/CRO & IRB	Notification as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
Device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate	Sponsor/CRO	Notification without unjustified delay after the investigator first learns of the device deficiency that might have led to an SAE.
Serious adverse events (SAE)	IRB	Per IRB reporting requirements
Withdrawal of IRB approval	Sponsor/CRO	Notification within 5 working days of withdrawal.
Progress Report	Sponsor/CRO & IRB	Periodic report detailing the progress of the study, occurring at least annually.
Deviations from protocol (CFR 812.150)	Sponsor/CRO & IRB	**Emergency Use:** Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Other:** If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from sponsor, the reviewing IRB, and FDA when required.
Failure to obtain informed consent	Sponsor/CRO & IRB	Notification within 5 working days
Final Report	Sponsor/CRO & IRB	Submitted within 3 months after termination or completion of the investigation.

12.1.5 Record Storage & Retention

Refer to the Clinical Trial Agreement for trial data storage, access, and retention requirements.

12.2 Data Management

Correction of missing or unclear data will be requested as necessary throughout the study. The CRO may request additional information including source documentation as needed. The CRO will also be responsible for confirming the overall integrity of the data. Refer to the study Data Management Plan for more details.

12.3 Device Accountability

All Lacrosse NSE ALPHA devices will be labeled with reference and lot numbers. Shipment and receipt records will be maintained, and upon receipt of the investigational devices, the site study coordinator (or delegate) will inventory the devices. As each subject receives treatment with the study device, the date of treatment, subject identifiers (site number/subject number), device assessment, and device traceability (e.g., unique identifiers) information will be recorded. If a study device is returned to the sponsor, the date of return and reason for the return shall be documented. Additional details regarding device management are referenced in the data management plan.

The Lacrosse NSE ALPHA devices must be stored in a secure location at each clinical site to ensure use only in the study, and unused devices must be returned promptly upon study completion or termination. Product labeled as “For Investigational Use Only” must only be used in the clinical investigation.

12.4 Site Qualification & Selection

The sponsor and/or CRO will assess each potential site to ensure the investigators and his/her staff meet the following criteria at minimum:

- The site has an interventional cardiologist that can act as principal investigator
- The Investigators are qualified by experience and training
- The site has adequate research support staff with the availability to fulfill the clinical study requirements specified in the protocol.
- The site is not participating in another investigational study that is currently enrolling subjects with competing eligibility criteria; studies that have completed enrollment and are in the subject follow-up phase would not exclude the site from participation in this study.
- The investigators are not on the FDA disqualified or debarred list.

Additional details are specified in the study-specific Site Qualification Questionnaires used to select eligible sites.

12.5 Site Training

Training of the clinical site personnel will be the responsibility of the study sponsor and the CRO. Site personnel will be trained per the study-specific Training Plan, which will consider numerous requirements, including inputs from the risk assessments described in this protocol. All site personnel will undergo training prior to performing any study-related procedures. All

training will be documented. Existing site personnel who have been delegated new tasks and new site personnel will undergo training as designated in the Training Plan.

12.6 Site Monitoring

This clinical study will be monitored according to a study-specific Monitoring Plan that complies with GCP. Monitors will assess for appropriate study conduct and data integrity, including review of eCRFs and parity checks with the source documentation, worksheets, and hospital charts. Periodic site visits will be conducted (either on-site or remotely), including a site initiation visit, routine monitoring visits, and a study closeout visit upon completion of the study. At a minimum, the ICF and the ICF process, primary and secondary endpoint data, and adverse event data will be 100% monitored and compared to source documentation. Monitoring will include comparison of eCRFs to source documentation for accuracy and appropriateness, study device accountability, review for unreported adverse events, and prompt evaluation of potential UADEs.

12.7 Institutional Review Board (IRB)

The sponsor will contract with a central IRB, making this service available to those sites able to use a central IRB. At a minimum, the CRO must have documented IRB approval for the protocol and the site-specific ICF prior to site activation to enroll subjects. The study (study number, protocol title, and version), documents approved (e.g., protocol, ICF), and the date of IRB review should be clearly stated on the IRB approval documentation signed by the IRB. The site will not be activated until a copy of written and dated IRB approval has been received by the CRO and other applicable study activation requirements are complete.

The site must submit any protocol or ICF amendments to the IRB and is required to forward a copy of the written approval to the CRO. An IRB approval of the amended document(s) must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF, if applicable. The IRB should also be informed of any event likely to affect the safety of subjects or the conduct of the study. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

The ICF must be reviewed by the CRO prior to submission to the IRB for approval.

12.8 Protocol Deviations

A protocol deviation is defined as a circumstance in which the investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Trial Agreement or Investigator Agreement).

Every attempt will be made to adhere to the protocol. However, should an investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the sponsor or CRO and IRB as soon as possible, but no more than 5 working days from the date the emergency occurred. Except for an emergent circumstance, prior approval from the sponsor, the IRB, and FDA (when

applicable) is required for any change in, or deviation from, the protocol as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects.

Protocol deviations will be documented on the Protocol Deviation eCRF. Deviations are reportable to the central or the institution's governing IRB during the annual reporting process, unless otherwise directed by the governing IRB requirements.

Repeated serious protocol deviations will be closely monitored by the CRO/sponsor. If excessive deviations or a failure to reduce deviations is noted, the sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations (21 CFR 812.46(a)).

12.9 Protocol Amendments

Changes to the protocol must be documented in a formal protocol amendment prior to implementation in the study. Amendments to the protocol will be initiated by the sponsor or CRO and must be approved by the IRB prior to implementation at the site.

12.10 Study Suspension or Termination

No formal statistical rule for early termination of this study for insufficient effectiveness of the study devices is defined.

The sponsor reserves the right to terminate or suspend the study for valid scientific reasons or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable risk to the subjects). The sponsor also reserves the right to terminate the study for business reasons. Refer to the Clinical Trial Agreement for specific information regarding study termination (by IRB withdrawal of approval, by PI, or by sponsor).

If the study is terminated prematurely or suspended, the sponsor will promptly inform all investigators of the termination or suspension and the reason(s). The IRB will also be informed, either by the sponsor or investigator, and provided with the reasons(s) for the termination or suspension. Regulatory authorities will be informed, as required.

The IRB may choose to discontinue the study at any site for which they granted approval if the research study is not conducted in accordance with the IRB's requirements or the research data indicates unexpected serious harm to subjects.

12.11 Subject Confidentiality

All information and data sent to the CRO concerning a subject or their participation in this study will be considered confidential. The sponsor, CRO, monitors, IRB, and regulatory representatives will have access to these confidential files and have the right to inspect and copy all records pertinent to this study for data verification. All data used in the analysis and reporting of this study will be without identifiable references to a subject. Subject names and contact information will be available to the sponsor, CRO, and monitors during review of medical records. Subject names may be available to the core laboratory and the CEC as they review study-related radiographic images and source documentation. This information will be treated

with adherence to professional standards of confidentiality. In addition, upon regulatory request, subject records shall be provided to U.S. regulatory agencies.

12.12 Audits & Inspections

Investigators and study sites are required to permit study-related monitoring, audits, IRB review, and regulatory inspection(s) and provide direct access to source data/documents.

12.13 Statements of Compliance

This study is to be conducted in compliance with the study protocol and in accordance with ethical principles that have their origin in the Declaration of Helsinki, as defined in the following U.S. and international standards for good clinical practice:

- International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2) (2016)
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 11, 50, 54 and 56 and 812) and HIPAA (45 CFR 164.508)
- ISO 14155:2020

12.14 Finance & Agreements

For details on how the clinical investigation is financed and the agreement between the sponsor, investigator(s), and site(s), refer to the Investigator Agreement and Clinical Trial Agreement.

12.15 Publications & Public Disclosure

Refer to the Clinical Trial Agreement for publications and public disclosure requirements and conditions.

12.16 Study Contacts

Refer to the Study Contact List for detailed contact information, including names, telephone numbers, and email addresses.

13.0 DEFINITIONS

13.1 Adverse Event Definitions

Adverse event: 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 and whether anticipated or unanticipated.

Adverse event relatedness: The relationship of an adverse event to the investigational device or the study procedure based on the categories defined below.

Relatedness	Description
Definitely	The adverse event follows a strong temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure. This can include an adverse event that occurs after the study procedure.
Probably	The adverse event follows a reasonable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, and the possibilities of other factors, such as underlying and concomitant illness, concomitant medications, or concurrent treatment can be excluded.
Possibly	The adverse event follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying or concomitant illness, concomitant medications, or concurrent treatment are presumable.
Unlikely	The adverse event has an improbable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying or concomitant illness, concomitant medications, or concurrent treatment.
Not related	The adverse event has no temporal sequence to the interventional procedure, the device treatment, or any user handling, or it can be explained by other factors, including underlying disease or concomitant illness, concomitant medication, or concurrent treatment.

Device deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. [*ISO 14155 2020, 3.19*]

- Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device.

Serious adverse event (SAE): An adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or a body function including chronic diseases
    - in-patient or prolonged hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event. *[ref. ISO 14155:2020, 3.45]*

Note: An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

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)*]

13.2 Other Study Definitions

Angiographic procedural success: Final diameter stenosis ≤ 50% in at least one of the Lacrosse NSE ALPHA attempted lesions following completion of the interventional procedure, including adjunctive stenting.

Cardiovascular death: Cardiovascular death is defined as death resulting from cardiovascular causes (Garcia-Garcia). The following categories may be collected:

- Death caused by acute MI
- Death caused by sudden cardiac, including unwitnessed, death
- Death resulting from heart failure
- Death caused by stroke
- Death caused by cardiovascular procedures
- Death resulting from cardiovascular hemorrhage
- Death resulting from other cardiovascular cause

Chronic total occlusion (CTO): 100% occlusions with TIMI 0 flow with at least a 3-month duration (Tajti).

Clinically-Driven Revascularization (Hicks): Revascularization is clinically-driven if the diameter stenosis is >50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia that cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:

- A history of angina pectoris, presumably related to the target vessel
- Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
- Abnormal results of any invasive functional diagnostic test (e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR))

Note: This definition is intended to be applied to TLR for determining clinically-driven status.

Comment: Target lesion revascularization of a >70% diameter stenosis by QCA in the

absence of the above signs or symptoms may be considered clinically-driven.

Clinically significant arrhythmia: Arrhythmias requiring intervention.

Dissection Classification System *[NHLBI 1989 classification system]*:

- Type A: Minor radiolucent areas within the coronary lumen during contrast injection with little or no persistence of contrast after the dye has cleared
- Type B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance
- Type C: Appear as contrast outside the coronary lumen ("extraluminal cap") with persistence of contrast after dye has cleared from the lumen
- Type D: Spiral ("barber shop pole") luminal filling defects, frequently with excessive contrast staining of the dissected false lumen
- Type E: Appear as new, persistent filling defects within the coronary lumen
- Type F: Dissections that lead to total occlusion of the coronary lumen without distal antegrade flow

  Note: Type E and F dissections may represent thrombus

Major adverse cardiac events (MACE): A composite of all-cause death, MI, and clinically indicated TLR. Classification of an event as a MACE will be performed by the CEC.

Minimum lumen diameter (MLD): The mean minimum lumen diameter (typically measured in-lesion, in-stent, and in-segment) derived from two orthogonal views by QCA (Jonas).

Myocardial infarction (MI): The ARC-2 definition of myocardial infarction (Garcia-Garcia) is as follows:

- Absolute rise in cardiac troponin (from baseline) ≥ 35 x upper reference limits *and*
- One or more of the following criteria
  - New significant Q waves or equivalent. Significant is defined as the development of new Q waves ≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads.
  - Flow-limiting angiographic complications
  - New "substantial" loss of myocardium on imaging

Perforation classifications (Ellis):

- Type I: Extraluminal crater without extravasation.
- Type II: Pericardial or myocardial blush without contrast jet extravasation.
- Type III: Extravasation through frank (≥ 1mm) perforation.

Procedural success: Successful delivery, inflation, deflation, and withdrawal of the study balloon without evidence of vessel perforation, flow limiting dissection (grade C or higher) or

reduction in TIMI flow from baseline that was related to the study device (per CEC adjudication) and final TIMI flow grade of 3 at the conclusion of the PCI procedure.

Reference vessel diameter (RVD): The average of normal segments within 10 mm proximal and 10 mm distal to the target lesion from two orthogonal views using QCA

Stent thrombosis: According to ARC-2 (Garcia-Garcia), definite stent/scaffold thrombosis is considered to have occurred by either angiographic or pathological confirmation and is defined as:

Definite stent thrombosis

Angiographic confirmation of stent/scaffold thrombosis:

- The presence of a thrombus[a] that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least one of the following criteria:
    - Acute onset of ischemic symptoms at rest
    - New electrocardiographic changes suggestive of acute ischemia
    - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)

Pathological confirmation of stent/scaffold thrombosis:

- Evidence of recent thrombus within the stent/scaffold determined at autopsy
- Examination of tissue retrieved following thrombectomy (visual/histology)

Probable stent thrombosis (Garcia-Garcia)

Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/ scaffold thrombosis and in the absence of any other obvious cause. (When the stented/scaffolded segment is in the left circumflex coronary artery or in the presence of preexisting electrocardiographic abnormalities (e.g., left bundle branch block, paced rhythms), definitive evidence of localization may be absent and CEC adjudication will be based on review of all available evidence.)

Silent stent/scaffold occlusion (Garcia-Garcia)

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.

[a] Occlusive thrombus: Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow within or proximal to a stent/scaffold segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

Target lesion: The treated segment including the 5 mm margin proximal and distal to the stent/scaffold (Garcia-Garcia).

Target lesion revascularization (TLR): A repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion (Garcia-Garcia).

Target vessel: The entire major intervened coronary vessel, including side branches (Garcia-Garcia).

Thrombolysis in myocardial infarction (TIMI) grading scale. ***[TIMI Study Group 1985]***

- TIMI 0 - no perfusion: There is no antegrade flow beyond the point of occlusion.
- TIMI I - penetration without perfusion: The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.
- TIMI II - partial perfusion: The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel – e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.
- TIMI III - complete perfusion: Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from uninvolved bed in the same vessel or the opposite artery.

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15.0 REVISION HISTORY

Rev.	Description of Changes	DCO #	Effective Date
A	Initial release.	2021-09-005	30Sep2021
B	Update to Study Population section to better define applicability to Medicare population; update several eligibility criteria to better clarify population; add a reference and update cross reference formatting.	2021-12-002	12/3/2021