The Lipid-Rich Plaque Study

LRP Study

SPONSOR:

INFRAREDX, INC.
34 THIRD AVENUE
BURLINGTON, MA 01803

VERSION: 1.10

ISSUE DATE: **26 DECEMBER 2013**

PRIMARY INVESTIGATOR:

RON WAKSMAN, MD
DIRECTOR, CARDIOVASCULAR RESEARCH AND ADVANCED EDUCATION
MEDSTAR HEART INSTITUTE
110 IRVING STREET NW, SUITE 4B-1
WASHINGTON, DC 20010
202-877-2812
RON.WAKSMAN@MEDSTAR.NET

CLINICALTRIALS.GOV: NCT02033694

LRP SYNOPSIS

Study Name: Lipid-rich Plaque (LRP) Study
Primary Purpose of the Study: The Lipid-rich Plaque Study will determine the relationship in patients undergoing IVUS-NIRS (near-infrared spectroscopy) imaging between lipid-rich plaque detected by intracoronary NIRS at non-stenotic sites and subsequent coronary events from new culprit lesions at both the patient level (vulnerable patients) and the segment level (vulnerable plaques).
Name of Device for Detection of Lipid-rich Plaque: The TVC Imaging system, which performs IVUS-NIRS imaging in a single pullback, is manufactured by InfraReDx, Inc. of Burlington, MA, USA. The TVC system is FDA approved for use to detect lipid core plaque and lipid core burden index, and to perform IVUS imaging for routine clinical purposes. NIRS has been used in over 5,000 patients world-wide in over 100 hospitals.
Study Leadership: **Principal Investigator, Worldwide:** Dr. Ron Waksman, Medstar Heart Institute, Washington, DC, USA **Principal Investigator, Japan:** Dr. Takashi Akasaka, Wakayama, Japan **Co-Principal Investigator, Japan:** Dr. Yasunori Ueda, Osaka, Japan **Principal Investigator, Europe:** Dr. Carlos Di Mario, London, England **Principal Investigator, Korea**: Dr. Seung-Jung Park, Seoul, Korea **Project Manager:** Rebecca Torguson, Medstar Heart Institute, Washington, DC, USA
Sponsor: Infraredx, Inc. Burlington, MA, USA **Statistical Consultant:** Dr. James Ware, Harvard School of Public Health, Boston, MA
Funding company: InfraReDx, Inc. Burlington, MA, USA Chief Medical Officer, Dr. James Muller Project Coordinator, Priti Shah
Study centers: Up to 100 sites world-wide (except in Scandinavia where PROSPECT II is being conducted with TVC).
Planned study period: 2014-2018
Background: The LRP Study is being initiated because of the success of both IVUS and NIRS in identifying vulnerable patients and vulnerable plaques. The PROSPECT Study and 4 additional IVUS studies have shown that plaques that occupy more than 70% of the area of the external elastic membrane (>70% plaque burden) as measured by IVUS have an increased likelihood of causing a coronary event. (Madder et al, JIC Supplement, 2013) While the IVUS success is based on size of a plaque, the novel NIRS system has shown promise based on analysis of plaque composition. The distinctive signature of a cholesterol plaque has now been found at the site of STEMI culprit lesions (Madder et al, JACC Interventions 2013). In addition patients with increased cholesterol in a non-culprit artery have been shown to have a 4-fold multivariate increase in the risk of a coronary event over the subsequent year. (Oemrawsingh et al, Journal of the American College of Cardiology, in press, 2014).

Objectives:

The Lipid-rich Plaque Study will be performed in patients undergoing IVUS-NIRS imaging (the index procedure) in whom a TVC catheter will be purchased and used for routine clinical indications. The study will test the ability of multi-vessel NIRS scanning for LRP in coronary segments without significant stenoses as a means to predict new coronary events arising from a new culprit lesion (a non-index culprit lesion). Analyses will be performed at both the patient level (vulnerable patients) and the segment level (vulnerable plaques).

If and when it is determined that vulnerable patients and vulnerable plaques can be detected by multi-vessel NIRS scanning, the study will transition from a detection study to a treatment study. This will require a separate protocol with separate IRB approval.

Methodology:

The LRP Study is a multicenter, prospective registry of patients with stable ischemic heart disease or a stabilized acute coronary syndrome (ACS) examined with angiography and IVUS-NIRS imaging for one or more suspected culprit lesions. After successful PCI of all angiographically flow-limiting lesions, intravascular imaging with the combined IVUS-NIRS catheter will be performed in all three coronary arteries if possible. Successful imaging of at least two vessels and a total of 50 mm of coronary artery is required for enrollment. All enrolled patients with a large LRP as detected by NIRS will be contacted at 2,6,12 and 24 months by phone to determine if a new coronary event has occurred. A randomly selected half of the patients with a small, or no, LRP will receive an identical follow-up. The origin of any new event will be determined by the follow-up angiography performed for clinical indications. The location of new culprit lesions will be identified and compared to the baseline NIRS findings in a central angiographic and NIRS-IVUS core laboratory located at MedStar.

Estimated number of subjects:

The goal is to enroll 9000 patients in the LRP Study. On the basis of the findings in the PROSPECT Study and the NIRS STEMI findings it is not expected that all 9,000 will be required to demonstrate successful prediction of coronary events with IVUS-NIRS imaging. If and when the goal of prediction is reached, the study will transition to a study of systemic and/or regional therapy of vulnerable patients and plaques.

Patient Enrollment and Procedure Overview:

Patients with stable ischemic heart disease or an ACS and planned coronary angiography in whom IVUS-NIRS imaging is likely to be performed will be asked to provide their consent for participation in the study. Angiography and PCI will be performed as clinically indicated. Unblinded NIRS IVUS imaging will be performed in the vessel, or vessels, containing a single or multiple suspected culprit lesions. Imaging for research purposes will begin in non-culprit vessels after all clinically indicated PCI has been performed. If a staged procedure is required to achieve revascularization of all lesions detected by angiography, the patient is not enrolled until after the staged procedure is successful and uncomplicated.

Imaging results in an artery not suspected to be a culprit will be blinded for NIRS, but not for IVUS.

The imaging goal, which may not be attainable in all cases, is to obtain IVUS-NIRS imaging from all 3 major coronary arteries.

The patient is formally enrolled in LRP after successful and uncomplicated PCI, and after the physician investigator determines that a total of at least 50 mm of IVUS-NIRS imaging data has been obtained from at least 2 major coronary arteries

Inclusion Criteria:

General Inclusion Criteria

1. Subjects presenting for coronary angiography in whom IVUS imaging is likely to be performed for clinical purposes.
2. Greater than 18 years of age.
3. Clinical presenting symptoms meeting one of the three criteria below:
    1. Subjects presenting with an acute coronary syndrome (ACS) including at least one of the following:
        a) Elevated cardiac biomarkers with CK-MB or troponin greater than upper limits of normal;
        b) ST depression or ST elevation >1mm in 2 or more contiguous leads in the absence of LVH, paced rhythm, BBB or early repolarization;
        c) A stabilized patient 24 to 72 hours post STEMI;
    2. Unstable angina pectoris;
    3. Stable angina pectoris and/or a positive functional study with evidence of ischemia.

Angiographic Inclusion Criteria

4. At least one Suspected Index Culprit Lesion requiring imaging with IVUS and/or NIRS for clinical indications.
5. At least two native epicardial coronary arteries (which may include the Suspected Index Culprit Artery) eligible for imaging with NIRS-IVUS.

Total IVUS/NIRS Imaging Inclusion Criterion

6. A minimum of a total 50 mm of coronary artery not involved in a prior or Index Procedure PCI (including the 5mm borders on either edge of the site receiving PCI) must be scanned. This 50mm total length may include contributions from the Suspected Index Culprit Arteries and from Index Non-Culprit Arteries. This total length must include contributions from two or more native imaged arteries.

Exclusion Criteria

1. Unstable patients (STEMI within the prior 24 hours; cardiogenic shock, hypotension needing inotropes, hypoxia needing intubation, and IABP) and patients that had a procedural complication (coronary dissection, perforation or a complication that would necessitate immediate-unplanned revascularization) during index PCI procedure.
2. History of CABG or planned CABG within 6 months following NIRS-IVUS imaging.
3. Patient has additional lesion(s) that needs a staged PCI.
4. Subject life expectancy is less than 2 years at time of index catheterization.
5. Subject with ejection fraction (EF) <30%.
6. Subject pacemaker dependent/paced rhythm.
7. Subject pregnant and lactating.
8. Any other factor that the investigator feels would put the patient at increased risk or otherwise make the patient unsuitable for participation in the protocol

9. Patients undergoing performance of PCI in all three major vessels during the index PCI.

Study follow-up:

All enrolled patients with a large LRP (Maximum Lipid Core Burden Index > 250 in 4 mm) will be contacted by phone by the study coordinator for each clinical site at 2, 6, 12 and 24 months to determine if a new coronary event has occurred. A randomly selected half of the patients with a small, or no LRP (Max 4mm LCBI< 250) will receive an identical follow-up. The determination of the need for follow-up will be made by the NIRS core lab after unblinding of the NIRS data and communicated to the clinical site prior to the 2 month follow-up.

The origin of any new event will be determined by the follow-up angiography performed for clinical indications. Clinical and imaging data for any follow-up event will be sent to the central angiographic and IVUS/NIRS core laboratory located at MedStar. The location of new culprit lesions will be identified by a clinical events committee (blinded to the baseline NIRS results), and compared to the baseline NIRS findings by the core laboratory.

Endpoints:

The primary outcome variable is Non-Index Culprit Lesion related Major Adverse Cardiac Events (NC-MACE) defined as the composite of:

- cardiac death,
- cardiac arrest,
- non-fatal myocardial infarction (MI),
- acute coronary syndrome,
- revascularization by CABG or PCI,
- rehospitalization for progressive angina, adjudicated to a non- index culprit lesion secondary to significant fixed, non-reversible (not-spasm related) lesion progression of more than 20% from the baseline study (confirmed by either serial angiography or by necropsy).

Statistical methods:

The study will test two primary hypotheses:

1)The Vulnerable Patient Hypothesis -- During a 24-month follow-up after IVUS-NIRS imaging, there will be an association between the baseline value of max 4mm LCBI (over all coronary artery segments included in the analysis) and the incidence of non- index culprit MACE events.

2) **The Vulnerable Plaque Hypothesis** – During a 24-month follow-up, there will be an association between the max 4mm LCBI of a proximal, mid, or distal segment of a coronary artery and the incidence of a follow-up culprit lesion in that segment leading to a Non Index Culprit-MACE event.

TABLE OF CONTENTS

STUDY CONTACT LIST

SPONSOR:

INFRAREDX, INC.
34 THIRD AVENUE
BURLINGTON, MA 01803
781-221-0053
Priti Shah
(pshah@infraredx.com)

PRINCIPAL INVESTIGATOR:

RON WAKSMAN, M.D.
MEDSTAR HEART INSTITUTE
110 IRVING STREET NW
SUITE 4B-1
WASHINGTON, DC 20010
202-877-2812
RON.WAKSMAN@MEDSTAR.NET

PROJECT MANAGEMENT:

REBECCA TORGUSON, MPH
MEDSTAR CARDIOVASCULAR RESEARCH NETWORK
110 IRVING STREET NW
SUITE 4B-1
WASHINGTON, DC 20010
202-877-2194
REBECCA.TORGUSON@MEDSTAR.NET

DATA MANAGEMENT:

MEDSTAR CARDIOVASCULAR RESEARCH NETWORK
110 IRVING STREET NW
SUITE 4B-1
WASHINGTON, DC 20010

NIRS, ANGIOGRAPHIC, AND IVUS CORE LABORATORY:

MEDSTAR CARDIOVASCULAR RESEARCH NETWORK
110 IRVING STREET NW
SUITE 4B-1
WASHINGTON, DC 20010

CLINICAL EVENT COMMITTEE, CHAIRPERSON:

MEDSTAR CARDIOVASCULAR RESEARCH NETWORK
110 IRVING STREET NW
SUITE 6B-4
WASHINGTON, DC 20010

1 DEFINITIONS

Major Adverse Cardiac Event (MACE) is

- cardiac death,
- cardiac arrest,
- non-fatal myocardial infarction (MI),
- acute coronary syndrome,
- revascularization by CABG or PCI,
- rehospitalization for progressive angina, adjudicated to a non-index-culprit lesion secondary to significant fixed, non-reversible (not-spasm related) lesion progression of more than 20% from the baseline study (confirmed by either serial angiography or by necropsy).

Follow-up Culprit Lesion -A lesion causing a Major Adverse Cardiac Event during the follow up period.

Non-Culprit Major Adverse Cardiac Event (NC-MACE) -A MACE that occurs due to a Follow-up Culprit Lesion not located at a site that underwent PCI at the time of Index Procedure.

PCI-related Major Adverse Cardiac Event (PCI-MACE) -As MACE that occurs due to a Follow up Culprit Lesion where the site of the Follow up Culprit Lesion is one in which PCI was performed at the index procedure.

Suspected Index Culprit Lesion is a lesion or multiple lesions requiring clinically necessary NIRS-IVUS interrogation at the time of the index procedure.

Index Suspected Culprit Artery -An artery or arteries that contains at least one Suspected Culprit Lesion at the time of the index procedure.

Index Culprit Lesion- A lesion considered to be responsible for the presenting symptoms at the time of the index procedure.

Index Non Culprit Artery - An artery that contains no culprit lesions at the time of the index procedure.

Large LRP - At least one 4 mm length of artery with a LCBI ≥ 250 as assessed by IVUS-NIRS imaging

Major Epicardial Arteries -The left anterior descending, left circumflex, and right coronary arteries and the branches associated with each.

Index procedure -The catheterization procedure that qualified the patient to be screened for this study.

2 INTRODUCTION

2.1 BACKGROUND AND RATIONALE FOR STUDY

Plaque composition rather than degree of stenosis has been shown to play a pivotal role in the development of plaque rupture leading to acute atherothrombotic events and sudden cardiac death. Vulnerable plaque is a term that represents "the susceptibility of a plaque to rupture" (1). Autopsy studies in patients who have died of cardiac causes have shown that the most common underlying plaque morphology is a ruptured thin-cap fibroatheroma (TCFA), with superimposed thrombosis (2). Although atherosclerosis is a pan-vascular process arising from systemic inflammation, vulnerable plaques are not present diffusely but are limited in number and are most commonly located in the proximal and mid segments of the epicardial coronary vessels (and distal in the right coronary artery) (3-5). Although several plaque types have been identified which are suspected to be prone to thrombosis, pathological studies conducted after events have occurred have found that the majority of culprit lesions are TCFAs, characterized by a large necrotic core with a thin (<65 μm) fibrous cap consisting of mostly type 1 collagen with few smooth muscle cells, infiltrated with macrophages and T lymphocytes (5,6). Cellular production of matrix metalloproteinases and other digestive enzymes, exacerbated by altered shear stress and focal cap calcification, are suspected to lead to plaque rupture, followed by tissue factor exposure and superimposed thrombus formation.

Most coronary events occur in individuals who would be classified as low or intermediate risk by the traditional risk factors contained in the Framingham risk score. Conversely, many individuals with an apparently adverse risk factor profile remain asymptomatic. Thus, for contemporary medicine to improve, the challenge is to find and treat those unrecognized individuals at highest risk without harming those who do not need treatment (limiting both under treatment and overtreatment). Given this pathophysiological background, the goal emerged to identify in vivo the structural, morphological, chemical, and physical properties of the such vulnerable plaques in patients, with the ultimate goal of preventing plaque rupture, thereby averting myocardial infarction (MI) and sudden cardiac death.
While the coronary angiography is the gold standard for identification of obstructive CAD, the angiogram is very limited for detection of vulnerable plaque. It provides only limited information about the underlying composition of coronary plaques. Direct visualization of atherosclerosis rather than merely identifying obstructive disease may improve risk stratification for future events. Therefore, a number of intravascular diagnostic modalities have been extensively tested over the last decade. Among those most widely tested are radiofrequency intravascular ultrasound, angioscopy, optical coherence tomography and near infrared spectroscopy (NIRS) (14).

PROSPECT is a prospective study of long-term outcomes in patients presenting with ACS. At baseline, 3-vessel angiography and intracoronary imaging with grayscale and RF-IVUS were performed to evaluate the characteristics of non-culprit lesions suspected to progress over time and cause major adverse cardiac events (MACE), defined as the composite of cardiac death, cardiac arrest, MI, unstable angina or increasing angina requiring re-hospitalization (7). By multivariable analysis, the only patient-level clinical variables independently associated with nonculprit lesion MACE during follow-up were insulin-treated diabetes and previous PCI (1). No angiographic variable was strongly associated with subsequent events. However, significant independent predictors of nonculprit lesion related MACE (i.e., events arising from those specific untreated lesions) were plaque burden ≥70% (hazard ratio [HR]: 5.03; p <0.001), the presence of a TCFA by RF-IVUS (HR: 3.35; p <0.001), and a minimal lumen area <4.0 mm2 (HR: 3.21, p < 0.001). The presence of 2 or 3 of these 3 characteristics identified lesions with a 10% and 18% likelihood, respectively, of an event arising from that site within 3 years (7). Conversely, the 3-year nonculprit lesion–related MACE rate in >1,650 IVUS lesions with none of these 3 characteristics was only 0.3%, and no events arose from coronary segments with <40% plaque area.

A recent summary of the effort to detect and treat vulnerable plaque noted that in 5 separate studies, a large plaque burden by IVUS has been associated with an increased risk of progression to a MACE culprit lesion, thus establishing the principle that vulnerable plaques can be detected. (Madder, Muller, Journal of Interventional Cardiology, Supplement, 2013). However the specificity of the detection has not been adequate to serve as a guide to therapy. A more accurate measure of suspected vulnerable plaques is needed.

As demonstrated by autopsy studies, cholesterol-rich atherosclerotic plaques, which are likely to be vulnerable plaques, have a specific near-infrared spectroscopic (NIRS) chemical signature. A TVC imaging system intracoronary catheter (InfraReDx, Inc., Burlington, Massachusetts) has been developed to identify this NIRS signature in coronary arteries of patients undergoing coronary angiography. This novel catheter uses rotation and an automated pullback to generate a longitudinal chemographic road map of the coronary artery that demonstrates the presence and location of lipid-rich plaque (LRP) whose presence could not be determined by coronary angiography. The NIRS capability has now been combined with a high-quality grayscale IVUS imaging system. The combined IVUS-NIRS catheter is FDA cleared and has obtained a CE mark. NIRS has been used in over 6,000 patients in over 80 hospitals world-wide for the detection of LRP. The safety experience for the IVUS-NIRS catheter is excellent with a profile similar to that of a standard IVUS catheter.

The algorithm identifies both “lipid-core plaque” (LCP) which is synonymous with “necrotic core plaque” (8-12) and “lipid pools” in which the cellular structure is intact, but an increased concentration of lipid is present. The inclusive term “lipid-rich plaque” (LRP) describes both lipid-core plaque and plaques containing lipid pools.

LRP appears to be the common thread linking plaque vulnerability and frank instability. It is also evident that LRP can be present in more than one artery since in many cases, atherosclerosis is a multifocal pan-coronary process (5,6). Hence delineation of plaque composition in both culprit and non-culprit lesions, and in multiple types of clinical presentations may be important. NIRS has been rigorously validated against autopsy specimens and is now established as a method to accurately identify LRP in patients (8,9).

NIRS has demonstrated that culprit lesions in patients with both non-ST elevation acute coronary syndrome (ACS) and in patients with stable angina frequently contain LRP (13). A recent study by Madder et al (JACC Interventions, 2013) demonstrated that large lipid-rich plaques, often circumferential and similar to those that will be tracked prospectively in the present study, were found at the culprit site in most patients experiencing an ST segment elevation myocardial infarction (STEMI) (14). The findings of Madder et al in 20 STEMI patients have now been reproduced in a larger group of 76 patients with STEMI studied in Sweden and in the US. (Erlinge et al, European Atherosclerosis Society Presentation, 2013). This cross-sectional study included a prospective test of the ability of a max 4mm LCBI > 400 to discriminate STEMI culprit lesions from other portions of the culprit artery. This measure was able to provide excellent discrimination, and will be utilized as a measure of a “suspected vulnerable plaque” in the prospective LRP Study.

In addition to this cross-sectional data, the NIRS signature of LRP has been linked to long-term coronary outcomes. A longitudinal study in 203 patients conducted by Omerawsingh et al demonstrated that the detection of LRP above the median in a non-culprit artery identified patients with a 4-fold increased risk of MACE over the subsequent year, thus detecting vulnerable patients (Omerawsingh et al, JACC, in press, 2013). In addition, linkages with angioscopic findings have been established. Ueda and colleagues at the Osaka Police Hospital compared angioscopic findings, which require the removal of blood to obtain a clear field of view, with NIRS findings which can be obtained more easily without the need for blood removal. Sites that were yellow by angioscopy also showed LRP as detected by NIRS. This equivalence is of particular importance because the finding of a yellow plaque by angioscopy has been proven to represent the finding of a vulnerable patient (Ohtani et al, Uchida et Am H J, 1995). These linkages with outcome studies, which build on the equivalence of angioscopy and NIRS, and represent only a small number of patients, require validation. This is the purpose of the larger, definitive LRP Outcomes Study.

2.1.1 STUDY AIMS

The aim of this global, multicenter, observational study is to evaluate the correlation between the presence of non-intervened, non-flow-limiting lipid-rich plaques detected by IVUS-NIRS imaging in two or more coronary arteries and the future development of a Major Adverse Cardiac Event (MACE) within the subsequent 24 months post imaging.

Endpoint: The primary outcome variable is Non-Culprit Major Adverse Cardiac Events (NC-MACE) defined as the composite of:

- cardiac death,
- cardiac arrest,
- non-fatal myocardial infarction (MI),
- acute coronary syndrome,
- revascularization by CABG or PCI,
- rehospitalization for progressive angina, adjudicated to a non index -culprit lesion secondary to significant fixed, non-reversible (not-spasm related) lesion progression of more than 20% from the baseline study (confirmed by either serial angiography or by necropsy).

Follow-up: All patients with a large LRP (defined as at least one 4 mm length of artery with a LCBI ≥ 250 as assessed by IVUS-NIRS imaging) will be followed for 24 months to determine the occurrence of MACE. Patients without a large LRP will be randomly allocated in a one to one ratio to a 24 month follow-up, or no follow-up.

Blinding: The results of NIRS imaging will be partially blinded to minimize the possibility that detection of excess lipid will lead to bias created by activities such as overtreatment of LRP and/or over-reporting clinical symptoms. Treatment of the Index Culprit Artery (or arteries) will be performed in an unblinded manner with full access by the clinical site to the results of IVUS-NIRS imaging. For NIRS imaging performed for research purposes in a non-culprit artery, the clinical site will be blinded to the NIRS results. The clinical site will not be blinded to the IVUS results in the non-culprit artery.

2.1.2 PRIMARY HYPOTHESES

Two hypotheses will be tested for plaques at non-stenotic sites that have not undergone PCI:

First, patients with increased max 4mm LCBI in all scanned arteries are more likely to experience NC-MACE than those without increased max 4mm LCBI (the vulnerable patient hypothesis);

Second, coronary artery segments (defined as the proximal, mid, and distal segments of the major epicardial arteries,) with increased max 4mm LCBI (within the segment) are more likely than segments without increased max 4mm LCBI to cause NC-MACE (the vulnerable plaque hypothesis).

The portion of the coronary artery or arteries to be studied will meet all of the following criteria:

- The portion of the coronary artery does not contain a flow-limiting stenosis, defined as > 50% diameter stenosis by visual angiographic estimate;
- The portion of the coronary artery has not undergone PCI in the past, and PCI is not performed at the index event or planned in a staged procedure. The length of artery excluded from the study because of PCI includes a 5mm border on either side of the intervened segment.

3 ENDPOINTS

3.1 PRIMARY BASELINE MEASUREMENTS AND ENDPOINTS

For the Test of the Vulnerable Patient Hypothesis

The primary baseline measurement will be the maximum LCBI in 4 mm (max 4mm LCBI) over all scanned portions of the coronary arteries. The portion of artery to be scanned will exclude sites in which PCI has been performed in the past or will be performed in the index procedure (also excluding 5 mm borders of any site that underwent PCI).

The primary endpoint for the test of the vulnerable patient hypothesis will be the incidence of NC-MACE within 24 months.

The primary hypothesis is that risk of NC-MACE will be positively associated with max 4 mm LCBI measured as a continuous variable. The exposure-response relationship will also be evaluated for max 4 mm LCBI expressed as a binary variable above and below varying thresholds. It is hypothesized that increasing levels of max 4mm LCBI will identify increasing levels of risk for the patient of experiencing NC-MACE within 24 months following the artery imaging.

For the Test of the Vulnerable Plaque Hypothesis

The primary baseline measurement will be the maximum 4 mm LCBI detected in each proximal, mid, or distal segment of coronary artery scanned. The portion of artery to be scanned will exclude sites in which PCI has been performed in the past or will be performed in the index procedure (including 5 mm borders of any site that underwent PCI).

The primary endpoint for the test of the vulnerable plaque hypothesis will be the incidence of NC-MACE within 24 months.

The exposure-response function will be calculated for varying levels of max 4mm LCBI for each coronary artery segment. It is hypothesized that increased levels of max 4 mm LCBI in a coronary artery segment will identify increased levels of risk for that segment of causing NC-MACE within 24 months following the artery imaging.

FOLLOW-UP

All patients with a large LRP (defined as at least one 4mm segment with a max LCBI ≥ 250 as assessed by IVUS-NIRS imaging) will be followed for 24 months to determine the occurrence of NC-MACE. Patients without at least one large LRP will be randomly allocated in a 1:1 ratio to 24 month follow-up or no follow-up.

3.2 SECONDARY AND TERTIARY ENDPOINTS AND SUBGROUP HYPOTHESES

The LRP Outcomes Study will produce a large amount of novel information that creates the opportunity for analysis of multiple secondary endpoints, multiple tertiary endpoints and multiple subgroups. Various methods of analysis and definitions of exposure, response and outcomes in subgroups of interest will be examined. Examples of each category and their relation to the primary endpoint are given below.

1) **Measures of exposure** – As stated above, the primary measure of exposure will be the Max 4mm LCBI. Additional analyses will be performed with the average LCBI, the IVUS plaque volume and other new measures of exposure that may emerge during the study.

2) **Outcomes** – The primary outcome will be NC-MACE (at the patient level in the Vulnerable Patient analysis and the segment level in the Vulnerable Plaque analysis) within 24 months following artery imaging.

3) **Methods of analysis** – As stated above, the primary method of analysis will involve estimation and testing for a positive association between max 4 mm LCBI and incidence of NC-MACE. Additional analyses of diagnostic performance will be performed for specific thresholds for max 4 mm LCBI, using the AUC and the net reclassification index as measures of performance.

4) **Subgroup analyses –** The relationship between exposure and response will be explored in patients with and without specific characteristics such as initial imaging presentation with ACS, diabetes, renal insufficiency, hypertension, age>65, male gender, and elevated cholesterol at baseline.

5) **Outcome at the Stented Site** While not a primary feature of the LRP Outcomes Study, an analysis will be performed of the impact of lipid status on the outcomes at the sited stented at the baseline study.

The LRP Study will test three secondary hypotheses about measures of patient-level risk derived from the NIRS chemogram, stated here in terms of the alternative hypothesis:

1) A threshold of max 4mm LCBI > 400 will identify patients at increased risk of a NC-MACE event.

2) An average LCBI in all scanned segments above the median will identify patients at increased risk of a NC-MACE event.

3) The exposure-response function described for the primary vulnerable patient analysis, viz, the relationship of max 4mm LCBI to NC–MACE, will demonstrate that higher values of max 4mm LCBI are associated with increased risk of the individual hard endpoints (non-culprit cardiac death, cardiac arrest, and non-fatal MI) included in the full NC-MACE endpoint.

The three pre-specified secondary hypotheses for the vulnerable-plaque level analysis are:

1) An average threshold of max 4mm LCBI > 400 in a coronary artery segment will identify patients at increased risk of a NC-MACE event caused by a culprit lesion located within that segment.

2) An average LCBI in a coronary artery segment above the median will identify sites at increased risk of a NC-MACE event due to a culprit lesion located in that segment.

3) Plaque burden >70% by grayscale IVUS plus a max 4mm LCBI>400 in a coronary artery segment will be a stronger predictor of risk that Max 4 mm LCBI>400 alone.

The following section provides written descriptions of additional tertiary hypotheses and exploratory analyses to be performed as part of the LRP Study:

3.3 TERTIARY ANALYSES FOR THE VULNERABLE PATIENT STUDY

- To assess the risk of MACE based on the max 4 mm LCBI observed in any scanned portion of the coronary arteries excluding all sites in which PCI has been performed (either at the index event, or earlier)
- To assess NC MACE risk with area under the curve (AUC) analysis of a receiver operator characteristic (ROC) curve for varying threshold values of Max 4 mm LCBI.
- To investigate whether the risk of a coronary event increases with the number (count) of LRP's with max 4mm LCBI > 400.
- To characterize the extent (LCBI) and size (max 4mm LCBI) of LRPs among enrolled patients with ACS vs non-ACS, and with and without diabetes.
- To determine the relationship between the extent of LRP (LCBI of scanned artery) and size of LRP (max 4 mm LCBI) and the timing to the MACE.
- To compare the IVUS study variables (plaque burden, remodeling index, and MLA) in patients with MACE versus IVUS study variables in a randomly selected group of patients without MACE. For this group the study segments will be assessed for IVUS, NIRS and QCA findings.
- To compare the IVUS variables with the NIRS findings for patients with MACE versus a randomly selected group without MACE.
- To assess the primary endpoint (described above) with the addition of a NIRS thin-cap algorithm to identify LRPs with thick and thin caps (if available).

3.4 TERTIARY ANALYSES FOR THE VULNERABLE PLAQUE STUDY

- To assess the relationship between the size of LRP in a coronary artery segment (max LCBI > 4mm) and MACE with an AUC analysis of an ROC curve.
- To determine whether the incidence of NC-MACE attributable to a Follow up Culprit Lesion at a given site is dependent on the LCBI of the 30 mm segment, excluding sites (and their borders) in which PCI was performed prior to or at the time of index procedure.
- To assess the relationship between the maximum 4 mm LCBI detected in each 10mm segment of coronary artery scanned and the appearance of a new culprit lesion within the corresponding 10 mm segment of artery. These 10 mm segments will exclude sites (and their borders) that underwent PCI prior to or during the index event.
- The 10 mm segments will be given a hierarchal level with the higher assignment to those 10mm segments closer to the proximal portion of the scanned artery.

4 STUDY POPULATION

Screening will be performed in patients presenting for coronary angiography in whom IVUS and/or NIRS evaluation is planned or could be utilized as a part of their clinically-indicated evaluation. Written informed consent will be sought prior to the catheterization procedure for those meeting the general inclusion and exclusion criteria.

IVUS-NIRS imaging for a Suspected Index Culprit Lesion or Lesions and all clinically necessary treatment of Suspected Index Culprit Lesion(s) will be performed per standard practice. Patients who have provided written informed consent will then undergo IVUS-NIRS imaging of the Index Non-Culprit Arteries for research purposes during the catheterization. Those in whom the Investigator determines that acceptable IVUS-NIRS imaging has been completed in at least 2 major epicardial coronary arteries of at least 50mm of cumulative imaged artery will then be enrolled into the study. Patients will be considered screen failures if NIRS IVUS scanning is not performed in at least 2 epicardial coronary arteries or less than 50mm of cumulatively imaged artery.

Blinding

As noted above, IVUS-NIRS imaging of the culprit artery (before and if necessary after PCI) will be performed in an unblinded manner with full access by the clinical site to the results of IVUS-NIRS imaging. For NIRS imaging performed for research purposes in the Index Non-Culprit Arteries, the catheterization laboratory team will be blinded to the NIRS results. The team will not be blinded to the IVUS results in the Index Non-Culprit Arteries.

4.1 NUMBER OF SUBJECTS

The total study enrollment will be 9,000 patients.

Eligible subjects for this study will meet ALL of the following inclusion and NONE of the exclusion criteria.

4.1.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria prior to enrollment in the study:

General Inclusion Criteria

1. Subjects presenting for coronary angiography in whom IVUS imaging is likely to be performed for clinical purposes.
2. Greater than 18 years of age.
3. Clinical presenting symptoms meeting one of the three criteria below:
    1. Subjects presenting with ACS defined as at least one of the following:
        a) Elevated cardiac biomarkers with CK-MB or troponin greater than upper limits of normal range;
        b) ST depression or ST elevation >1mm in 2 or more contiguous leads in the absence of LVH, paced rhythm, BBB or early repolarization;
        c) A stabilized patient 24 to 72 hours post STEMI;
    2. Unstable angina pectoris;
    3. Stable Angina Pectoris and/or a positive functional study with evidence of ischemia.

Angiographic Inclusion Criteria

4. At least one Suspected Index Culprit Lesion requiring imaging with IVUS and/or NIRS for clinical indications.

5. At least two native epicardial coronary arteries (including the Suspected Index Culprit Artery) eligible for imaging with NIRS-IVUS

Total IVUS/NIRS Imaging Inclusion Criterion

6. A minimum of a total 50 mm of coronary artery not involved in a prior or Index Procedure PCI (including the 5mm borders on either edge of the site receiving PCI) must be scanned. This 50mm total length may include contributions from the Suspected Index Culprit Arteries and from Index Non-Culprit Arteries. This total length must include contributions from two or more native imaged arteries.

4.1.2 EXCLUSION CRITERIA

Subjects must meet none of the following exclusion criteria prior to enrollment:
General Exclusion Criteria

1. Unstable patients (STEMI within the prior 24 hours; cardiogenic shock, hypotension needing inotropes, hypoxia needing intubation, and IABP) and patients that had a procedural complication (coronary dissection, perforation or a complication that would necessitate immediate-unplanned revascularization) during index PCI procedure.
2. History of CABG or planned CABG within 6 months following NIRS-IVUS imaging.
3. Patient has additional lesion(s) that needs a staged PCI.
4. Subject life expectancy is less than 2 years at time of index catheterization.
5. Subject with ejection fraction (EF) <30%.
6. Subject pacemaker dependent/paced rhythm.
7. Subject pregnant and lactating.
8. Any other factor that the investigator feels would put the patient at increased risk or otherwise make the patient unsuitable for participation in the protocol.
9. Patients undergoing performance of PCI in all three major vessels during the index PCI.

4.2 REVIEW OF CHEMOGRAM TO DETERMINE PROTOCOL FOR FOLLOW-UP DEPENDING ON THE PRESENCE OR ABSENCE OF A LARGE LRP

At the end of the index procedure the chemogram (the NIRS findings output) data for both the Suspected Index Culprit Lesion or Lesions (unblinded) and Index Non-culprit (blinded) Arteries will be submitted to the NIRS Core Laboratory for evaluation. The Core Lab will review the chemogram to determine if a large LRP is present in an area that:

1) had not undergone PCI in the past,
2) did not undergo PCI at the time of the index procedure.

Areas that have undergone PCI (stent, balloon or other device) plus a 5 mm border on either side of the intervened area will be excluded from analysis.

A “large LRP” will be defined as a 4mm segment within the eligible area with an LCBI ≥ 250.

The Large LRP Group: All patients with a large LRP will be followed with a phone inquiry at 2,6,12 and 24 months post enrollment.

The Small or No LRP Group: Of this group, 50% will be randomly assigned (in a 1:1 fashion) to be followed with a phone inquiry at 2,6,12 and 24 months post enrollment.

The follow-up status for each patient will be determined by the core lab and communicated to the site coordinator prior to the 2 month follow-up window for the call. The clinical site will remain blinded to the NIRS findings, as will the clinical events committee.

It is anticipated that approximately 1/3 of the 9,000 patients will have a large LRP, leading to complete follow-up in 3,000 patients with a large LRP and 3,000 with a small or no LRP.

5 STUDY DESIGN

This is a prospective, multicenter, international study that will enroll 9,000 patients presenting for a clinically indicated cardiac catheterization with IVUS-NIRS interrogation for a culprit or suspected-culprit lesion. Patients will be screened for enrollment into the study after they provide written informed consent and undergo IVUS-NIRS imaging of at least 2 coronary arteries, including the Index Culprit Artery. If PCI is performed during the index procedure, the artery length for study inclusion will exclude the segment undergoing PCI plus a border of 5mm on either side of the PCI treated segment. Patients in whom IVUS-NIRS imaging is performed in only one artery will be considered screen failures.

It is expected that IVUS-NIRS imaging of the Suspected Index Culprit Artery will be performed for routine clinical indications. For this reason both NIRS and IVUS data from the culprit artery will be available in an unblinded fashion to the clinical site.

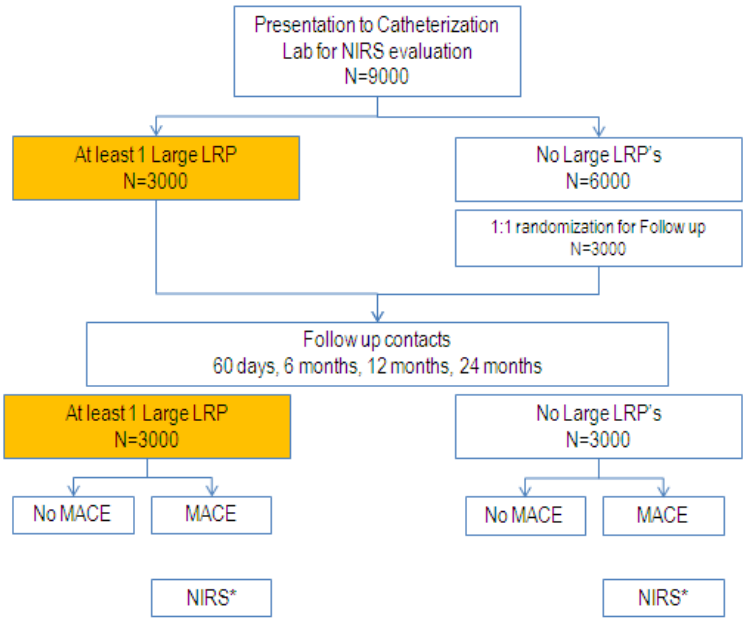
IVUS imaging of Index Non-Culprit Arteries may be of immediate clinical value (detection of an unexpected stenotic area) while NIRS imaging of Index Non-Culprit Arteries will be performed for research purposes. Hence for the Index Non-Culprit Arteries, IVUS data will be available to the clinical site, but NIRS data will be blinded.

Follow-up will be conducted in 6,000 patients (as defined in figure 1) at 2,6,12 and 24 months to determine the occurrence of a NC-MACE and the relationship of a Follow up Culprit Lesion to the baseline characteristics of the coronary artery segment.

The expected 9,000 patients will be enrolled at up to 100 centers throughout the world. It is expected that enrollment for the LRP Study will start in January, 2014 and conclude in or around December, 2015. Therefore, follow-up for the last patient enrolled will conclude in December 2017.

If the goals of the study – identification of vulnerable patients and vulnerable plaque by IVUS-NIRS imaging – are achieved before the enrollment of 9,000 patients, the study will transition to a blinded, randomized study of the use of IVUS-NIRS imaging to guide treatment.

Figure 1: Proposed flow of patients in the Lipid-rich Plaque Study



*if available

5.1 STUDY ASSESSMENTS AND PROCEDURES

5.1.1 STUDY SCHEDULE

Table 1: Schedule of Contacts

	Index	60 days (± 14 days)	6 months (± 14 days)	12 months (± 14 days)	24 months (± 30 days)
Patient Data*	X				
Procedural details	X				
TVC Imaging	X				
Angiogram submission$	X	X$	X$	X$	X$
NIRS/IVUS submission$	X	X$	X$	X$	X$
Adverse Events	X				
MACE	X	X	X	X	X

*Demographics, medical history and risk factor review; $angiograms and NIRS IVUS data will be collected if MACE occur (no protocol driven follow up catheterization or protocol driven TVC will be performed). Patients with no large LRP who are not randomly assigned to the 2 year follow-up will still have their baseline data and procedural data recorded and submitted for analysis.

5.1.2 VISITS

5.1.2.1 INDEX VISIT

Screening:

As described above (Section 4) screening will be performed in patients presenting for coronary angiography in whom IVUS and/or NIRS evaluation is planned or could be utilized as a part of their clinically-indicated evaluation. Written informed consent will be sought prior to the catheterization procedure for those meeting the general inclusion and exclusion criteria.

IVUS-NIRS imaging for a Suspected Index Culprit Lesion or Lesions and all clinically necessary treatment of Suspected Index Culprit Lesion(s) will be performed per standard practice. Patients who have provided written informed consent will then undergo IVUS-NIRS imaging of the Index Non-Culprit Arteries for research purposes during the catheterization. Those in whom the Investigator determines that acceptable IVUS-NIRS imaging has been completed in at least 2 major epicardial coronary arteries of at least 50mm of cumulative imaged artery will then be enrolled into the study. Patients will be considered screen failures if NIRS IVUS scanning is not performed in at least 2 epicardial coronary arteries or less than a cumulative 50mm of artery is imaged.. No additional data will be collected on such patients.

Enrollment:
Patients with a successful IVUS-NIRS scan of >50 mm length in 2 or more arteries will be enrolled in the Study. IVUS-NIRS should be performed in 2 or more major epicardial arteries as mentioned above including the culprit artery.
The portion of the coronary artery or arteries to be studied will meet all of the following criteria:

- The portion of the coronary artery does not contain a flow-limiting stenosis, defined as > 50% diameter stenosis by visual angiographic estimate;
- The portion of the coronary artery has not undergone PCI in the past, and PCI is not performed at the index event or planned in a staged procedure. The length of artery excluded from the study because of PCI includes a 5mm border on either side of the intervened segment.

Suspected Index Culprit Lesion or Lesions -- IVUS-NIRS Assessment:

For a native artery deemed by the physician to require clinically-indicated IVUS interrogation, the TVC console will image and record the IVUS and NIRS findings in an unblinded fashion (meaning, both the IVUS and NIRS images and details as provided on the commercially available TVC system will be available to the clinical site for diagnosis and treatment of the artery). The TVC system will display the images and details for all pull-backs performed within the Suspected Index Culprit Artery throughout the imaging and, if needed, for treatment of the Index Culprit Artery. The denotation of “suspected culprit’ and ‘culprit’ will be recorded on the case report form.

Once the clinical team determines that all of the clinically-indicated IVUS has been completed, the clinical team will switch the TVC System to the NIRS-blinded mode, as specified in the Manual of Operations for the LRP Study.

Index Non-Culprit Artery or Arteries -- IVUS-NIRS Assessment:

For an artery that does not require clinically-indicated IVUS imaging, the TVC console will image and record the NIRS findings in a blinded fashion, only displaying the IVUS findings to the clinical site (meaning, only the IVUS images and details as provided on the commercially available TVC system will be available to the physician). The denotation of ‘non-culprit’ will be recorded on the case report form.

5.1.3 ALLOCATION TO FOLLOW UP

For patients who are enrolled, the IVUS-NIRS images will be submitted to the NIRS Core Laboratory within 5 business days of collection and enrollment. The NIRS Core Lab will then assess the totality of NIRS findings, excluding locations and 10 mm borders of locations that underwent PCI, to establish the patient level max 4mm LCBI of all scanned segments. The NIRS Core Lab determination that the per patient max 4mm LCBI is below 250 will indicate that the patient will be randomized to follow-up or no follow-up. Patients with values above > or = to 250 will all receive follow-up per figure 1. The NIRS Core Lab will provide notification to the site prior to the 60 day follow up time interval to indicate to the sites which patients require follow up. The patient will be allocated as below:

- Patients with a max 4mm LCBI of all scanned segment ≥ 250 will be followed for a 2 year period as described in section 5.1.3.
- Patients with a max 4mm LCBI of all scanned segment < 250 will be randomized to follow up or no follow up beyond hospital discharge. Patients randomized (in a 1:1 fashion) to follow up will be followed for a 2 year period as described in section 5.1.3. The allocation will occur within the electronic case report form system and will take into consideration the site and have a set block size to help mitigate unequal allocation by site. Patient allocated to no follow up beyond hospital discharge will only have data collected through hospitalization within the electronic case report form.

The NIRS findings from the Index Non-culprit Artery details including the Core Lab determined patient-level max 4mm LCBI will be blinded to the clinical site.

5.1.4 FOLLOW UP

Follow up:

The site will be notified prior to the 60 day follow up window whether or not the patient requires follow up per the algorithm listed in section 5.1.2.2, Allocation to Follow up. The NIRS Core Lab will notify the enrolling site of the follow up allocation without unblinding the max 4mm LCBI per patient value.

Patients allocated to the 24 month follow up group will undergo clinic or telephone contact or medical record review at 60 days (± 14 days), 6 months (± 14 days), 12 months (± 30 days) and 24 (± 30 days) months. The follow up will include the review for the occurrence of NC-MACE following hospital discharge from the Index Procedure or the last follow up. If the lipid profile was clinically evaluated following hospital discharge from the Index Procedure or the last follow up, these values will be recorded within the electronic case report form.

Patients will have essential data collected at the time of index enrollment. These data will be collected by an electronic data capture system.

NC-MACE Occurrence:

Once an event has been identified by the coordinator, additional source documentation regarding the event will be collected. These data will be submitted to the Clinical Event Committee for adjudication to confirm that a NC-MACE has occurred, and, if possible, to identify the site of the Follow up Culprit Lesion causing the event. Such supporting documents will include, but not be limited to:

Death certificates, autopsy reports, discharge summaries, relevant progress notes from rehospitalizations for ischemia or angina, catheterization reports, surgical reports, angiograms (films), re-imaging (films), etc.

5.1.5 ANGIOGRAM ACQUISITION GUIDELINES

Angiographic imaging will be performed per standard of care; however, the following items should be included on the fluoroscopy during the catheterization for all non-culprit arteries:

- All catheters used throughout the procedure should be clearly visualized in the diagnostic cines with a straight (non-tapered) portion of the unfilled catheter for off-line image calibration. The catheter and segment of interest should be centered in the image. At least 1 cardiac cycle, before contrast injection, should be recorded for calibration of empty catheter tip.
- Qualitative and quantitative analysis will be performed using at least 2 (two) orthogonal angiographic views of the lesion.
- Intracoronary NTG is not required. However, if given during the procedure usage will be recorded on the angiographic technician's worksheet.
- If a PCI is pursued during the procedure this will be noted on the angiographic technician's worksheet.
- All catheter sizes used during the catheterization should be recorded as specified above and listed on the angiographic technician's worksheet.
- Images of the TVC™ IVUS-NIRS catheter distal and proximal placements should be recorded by fluoroscopy and recorded on the angiographic technician's worksheet for each run performed.

5.1.6 TVC™ CORONARY IVUS-NIRS IMAGING GUIDELINES

All IVUS-NIRS imaging will be performed, either in the culprit or non-culprit arteries utilizing the automatic, motorized pullback device. The IVUS-NIRS catheter should be positioned as distal as clinically feasible within each vessel. The pull back should continue as proximal as clinically feasible. Fluoroscopy capture of the IVUS-NIRS catheter marker positioning should be recorded on cine run prior to initiation of the automatic, motorized pull back; this should then be repeated upon completion of the pull back. The pull back start and stop time for both Suspected Index Culprit Lesion and Non-Culprit Arteries will be recorded within the case report form.

Within each native epicardial artery the maximum suitable distance of artery will be imaged. All study artery/vessel imaging will occur using the automatic pullback transducer at a rate of 0.5mm/second.

<u>Suspected Index Culprit Lesion or Lesions -- IVUS-NIRS Assessment:</u>

For a native artery deemed by the physician to require clinically-indicated IVUS interrogation, the TVC console will image and record the IVUS and NIRS findings in an unblinded fashion (meaning, both the IVUS and NIRS images and details as provided on the commercially available TVC system will be available to the clinical site for diagnosis and treatment of the artery). The TVC system will display the images and details for all pull-backs performed within the Suspected Index Culprit Artery throughout the imaging and, if needed, for treatment of the Index Culprit Artery. The denotation of "suspected culprit' and 'culprit' will be recorded on the case report form.

Once the clinical team determines that all of the clinically-indicated IVUS has been completed, the clinical team will switch the TVC System to the NIRS-blinded mode, as specified in the Manual of Operations for the LRP Study.

<u>Index Non-Culprit Artery or Arteries -- IVUS-NIRS Assessment:</u>

For a artery that does not require clinically-indicated IVUS imaging, the TVC console will image and record the NIRS findings in a blinded fashion, only displaying the IVUS findings to the clinical site (meaning, only the IVUS images and details as provided on the commercially available TVC system will be available to the physician. The denotation of 'non-culprit' will be recorded on the case report form.

The processes for establishing the TVC system to blind the NIRS findings on the console are located in the Manual of Operations for the LRP Study.

Study Segment(s):
The portion of the coronary artery or arteries to be studied will meet all of the following criteria:

- The portion of the coronary artery does not contain a flow-limiting stenosis, defined as > 50% diameter stenosis by visual angiographic estimate;
- The portion of the coronary artery has not undergone PCI in the past, and PCI is not performed at the index event or planned in a staged procedure. The length of artery excluded from the study because of PCI includes a 5mm border on either side of the intervened segment;

For the off-line Core Laboratory NIRS analysis will include the following definitions for the vulnerable plaque-based primary endpoint evaluation.

For each coronary artery with available IVUS-NIRS imaging, the proximal segment will be defined as the first 30mm of the proximal chemogram obtained in that vessel, the mid segment as the next 30mm, and the distal segment as the remaining chemogram up to a 30mm segment. If the total chemogram of a vessel exceeds 90 mm, the segment beyond 90 mm will be defined as the far distal segment. This anatomic specificity will be important in the Vulnerable Plaque analysis, as described below.

Additionally, the coronary artery analysis will be broken into 10mm segments in a similar hierarchal fashion as mentioned above for the 30mm segment analysis. This 10mm segmentation in a hierarchal fashion within each epicardial vessel will be analyzed as a tertiary endpoint.

5.2 STUDY WITHDRAWAL

The only acceptable reason for withdrawal from the study is the subject's (or legal guardian's) withdrawal of consent. All reasons for withdrawal (if given) will be recorded in the source documentation.

5.3 PROTOCOL VIOLATIONS

All deviations from clinical protocol requirements, including ICH/GCP guidelines referred to in this protocol, will be considered protocol violations. A 'serious violation' is one that may affect the scientific soundness of the protocol or one that would affect the rights, safety, or welfare of the subjects.

Subject level deviations are those that occur in direct association with a specific study subject. These include, but are not limited to, deviations from Informed Consent procedures, inclusion/exclusion criteria, required clinical assessments.

6 STATISTICAL CONSIDERATIONS

6.1 STATISTICAL ANALYSIS

The Lipid-rich Plaque Outcomes Study is a global, multicenter prospective cohort study of patients who have undergone IVUS-NIRS coronary imaging to determine the extent and size of non-flow-limiting LRP's in their

coronary arteries. The objective of the study is to determine whether the presence of one or more LRPs is predictive of subsequent coronary events. A patient-level (Vulnerable Patient) and a plaque-level analysis (Vulnerable Plaque) will be conducted.

Primary Hypotheses:

The study will test two primary hypotheses, stated here in terms of the null hypothesis:

H1: Vulnerable Patient Hypothesis – During 24-month follow-up after IVUS-NIRS imaging, there will be no association between the baseline value of max 4mm LCBI (over all coronary artery segments included in the analysis) and the incidence of non-culprit NC-MACE events. (This hypothesis will be tested with a time-to-event analysis as described below).

H2: Vulnerable Plaque Hypothesis – During 24-month follow-up, there will be no association between the max 4mm LCBI of the proximal, mid, or distal segment of a coronary artery and the incidence of a culprit lesion in that segment leading to a NC-MACE event.

Additional Objectives:

As noted above, the study will also investigate the prognostic value of multiple novel NIRS measures and conventional IVUS measures that can be evaluated in multiple ways.

Statistical Methods:

To test Hypothesis 1 (the Vulnerable Patient Hypothesis), we will first fit a univariate proportional hazards regression model in which max 4mm LCBI is the only independent variable and NC-MACE is the outcome. The null hypothesis will be tested by the Wald test that the regression coefficient in a proportional hazards regression model is significantly different from 0. This analysis will determine whether max 4mm LCBI is a risk factor for NC-MACE. In supportive analyses, we will assess the validity of the proportional hazards assumption. We will also investigate the predictive value of the binary variables defined by varying cut-points of max 4mm LCBI. The analyses using these cut-points will be used to calculate an ROC curve characterizing the prognostic value of presence of a lipid-rich plaque. Weighted estimation will be required to estimate the ROC curve because of the underrepresentation of 3,000 individuals (absence of follow-up data) with no segments with max 4mm LCBI ≥ 250 in the follow-up cohort.

In multivariate analysis, we will assess the incremental prognostic value of lipid-rich plaques by fitting proportional hazards regression models that include the max 4mm LCBI value and other identified prognostic variables. To identify the variables to be included in the multivariate model, we will perform a step-up regression blinded to the NIRS and IVUS data to identify the prognostic factors other than NIRS or IVUS data associated with the NC-MACE outcome. When that model has been selected, max 4mm LCBI will be added to the model to assess its incremental prognostic value. This will be the definitive test of Hypothesis 1. Results from these analyses will be used to estimate the net reclassification improvement, a measure of the incremental prognostic value of a new prognostic variable. Weighted estimation will also be required to calculate the NRI. Other covariates to be considered as possible prognostic factors in the NRI analysis include but are not limited to age (10 year units), hypertension, diabetes (any), current smoking (at the time of NIRS evaluation), prior history of coronary disease, history of cardiovascular disease, BMI, index catheterization presentation status (ACS, unstable angina, stable angina, and positive EST), total cholesterol level, use of statin therapy at discharge (as well as prior to index catheterization), requirement for at least 1 lesion treatment at the time of index catheterization), ADP antagonist at discharge, plasma lipid levels at baseline and during follow-up if available and history of renal insufficiency.

In a secondary statistical analysis, we will investigate whether the location of a large LRP within a blinded or non-blinded NIRS recording modifies its association with subsequent NC-MACE events.

To test Hypothesis 2 (the Vulnerable Plaque Hypothesis), we will treat the individual coronary artery segments as separate units of observation, with appropriate adjustment for clustering of segments within patients. A study participant will typically provide results for up to 9 segments. To test this hypothesis, we will fit a proportional hazards regression model with max 4mm LCBI in the coronary artery segment as the measure of exposure and NC-MACE during 24 months caused by a new culprit lesion in that segment as the outcome. All models will include a categorical variable representing the type of coronary artery segment. To identify other characteristics of the coronary artery that should be included in this analysis, we will perform an initial analysis blinded to the value of max 4mm LCBI to determine whether segment type, segment length, or other characteristics of individual segments are risk factors for NC-MACE. Identified segment characteristics will be included in the model used to test the primary hypothesis. All analyses of coronary artery segments will use generalized estimating equations with robust variances to account for clustering of segments within patients.

As in the vulnerable patient analysis, we will investigate the predictive value of the binary variables defined by varying cut-points of max 4mm LCBI. The analyses using various cut-points will be used to calculate an ROC curve characterizing the prognostic value of presence of a lipid-rich plaque in a coronary artery segment. Weighted estimation will be required to estimate the ROC curve because of the exclusion from follow-up of 3,000 of the 9,000 enrolled patients with no segments with max 4mm LCBI ≥ 250 in the follow-up cohort and analyses will account for clustering of segments within patients.

Results from the multivariate analyses will be used to estimate the net reclassification improvement obtained by considering max 4mm LCBI of individual segments as a risk factor. Weighted estimation will again be required to calculate the NRI. The covariates considered in the vulnerable patient analysis will again be considered in the vulnerable plaque analysis.

6.2 SAMPLE SIZE CONSIDERATIONS

A total of 9,000 patients will be enrolled with multi-vessel scans. It is expected based on the PROSPECT Study that at least 720 patients (8%) will experience a NC-MACE event. We expect to find approximately 3,000 patients with large LRP (max 4mm LCBI ≥ 250). All 3,000 of these patients will be followed with phone calls for 2 years to identify those who have an event. We expect to observe at least 300 events in this group. From the 6,000 with no or small LRP, a random sample of 3,000 patients will also be followed to determine their event rate, and to examine with IVUS and angiograms those in whom events occur. Of the approximately 2,700 patients with large LRP who do not have an event, a 300 person sample will be selected for IVUS and angiographic analysis to investigate characteristics of the yellow spots that did not lead to events.

Vulnerable Patient Analysis

For hypothesis 1, we will test the hypothesis that there will be no association between the baseline value of max 4mm LCBI (over the entire area scanned) and the incidence of NC-MACE.

In PROSPECT registry results, the 24-month cumulative incidence of NC-MACE in patients was approximately 10%. Subsequent STEMI literature indicates that patients with large LRP will have a higher rate than that observed in PROSPECT.

For the power calculations below, we assumed 6,000 evaluable patients, an event rate between 4 and 8% in the overall LRP study, and a two-sided alpha of 0.05 with a standard deviation of 100 for max 4mm LCBI. Table 2

provides values for the power of the study to detect the following effect sizes: hazard ratio of 1.18, 1.20, and 1.22 per 100 unit increase in max 4mm LBCI (calculated in PASS 12). These results demonstrate that the study will have 80% power to detect a minimal effect size of 1.18 per 100 unit increase in the max 4mm LCBI with 6,000 patients and an overall cumulative incidence of 5% at 24 months. As described in section 5.3, interim analyses will be performed at 6 month intervals.

Table 2: Hypothesis 1: Power Calculation for Vulnerable Patient Hypothesis

2 Year cumulative incidence	Relative Risk per 100 unit increase in max 4mm LCBI		
overall, patient level	1.18	1.20	1.22
8%	*0.95*	*0.98*	*0.99*
7%	*0.92*	*0.96*	*0.98*
6%	*0.88*	*0.93*	*0.97*
5%	***0.82***	*0.88*	*0.93*
4%	*0.73*	*0.81*	*0.87*

Vulnerable Plaque Analysis

For hypothesis 2, we will test the hypothesis that there will be no association between the baseline value of max 4mm LCBI of the proximal, mid, or distal segment of a coronary artery and the incidence of NC-MACE.

For the vulnerable plaque analysis, we assumed that a patient will have a minimum of 50 mm of scanned target artery within at least 2 native epicardial arteries, yielding a minimum of 4 segments. Assuming that 24,000 segments (from 6,000 patients) will be available for analysis, a two sided alpha of 0.05 and a standard deviation of 100 LCBI units for max 4mm LCBI, Table 3 provides values for the power of the study to detect the following effect sizes: hazard ratio of 1.18, 1.20, and 1.22 (calculated by PASS 12). The study will have 80% power to detect a minimum effect size of 1.18 per 100 unit increase in the max 4mm LCBI with the minimum expected number of segments (24,000) and an overall cumulative incidence of 1.25% within the segments at 24 months.

Table 3: Hypothesis 2: Power Calculation for Vulnerable Plaque Hypothesis

2 Year cumulative incidence	Relative Risk per 100 unit increase in max 4mm LCBI		
overall, segment level	1.18	1.20	1.24
1.75%	0.92	0.96	0.98
1.50%	0.88	0.93	0.97
1.25%	**0.82**	0.88	0.93
1.00%	0.73	0.81	0.87
0.75%	0.60	0.69	0.76

6.3 INTERIM ANALYSIS PLAN

As is evident from the power calculations provided in Section 5.2, for both the patient and segment level analysis, the LRP Study will have excellent power to detect relatively small increases in risk due to the presence of LRP.

The PROSPECT Study, with 700 patients, detected a hazard ratio of 5 for the presence of plaque burden > 70%. If the hazard ratio for increased LCBI reaches or exceeds 5, the LRP Study will provide definitive evidence that max 4mm LCBI predicts NC-MACE well before 6,000 patients have completed two-year follow-up. To provide an

opportunity for an early decision if this should occur, the LRP Outcomes Study will employ an interim analysis plan as described below.

When criteria for demonstrating an association between max 4mm LCBI and risk of NC-MACE have been met, the LRP Study will transition to a treatment study. This treatment study will include a control arm in which more detailed questions regarding the prognostic value of LCBI in various subgroups can be addressed in great detail.

The transition to a treatment study will require submission of a new protocol to the IRBs of the participating centers.

The interim analysis plan for the LRP Outcomes Study will be based on the Pocock spending function for repeated significance testing. This spending function will provide a greater opportunity for early stopping if strong associations emerge than would the O'Brien-Fleming or Haybittle-Peto spending functions. Specifically, review of accumulated data by the Data and Safety Monitoring Committee (DSMB) will occur on December 1, 2014 and at 6 month intervals thereafter until December 1, 2016. The DSMB will review the accumulated data to determine whether, in the multivariate analyses described in Section 5.1, both the vulnerable patient and the vulnerable plaque null hypotheses are statistically significant at the level required by the adjustment for repeated testing provided by the Pocock procedure. If those conditions are met, the DSMB may recommend termination of the study. If the study continues to the planned completion of two-year follow-up of all patients enrolled in the follow-up study, the two null hypotheses will be tested at the same significance level as that employed in the interim analyses. Additional information regarding the interim analysis plan will be provided in the Statistical Analysis Plan (SAP).

7 ADVERSE EVENTS

The IVUS-NIRS TVC catheter is designed to function as a conventional, rotating core, IVUS catheter which has an excellent safety record. Experience with NIRS in over 5,000 patients has shown that the TVC catheter safety profile does not differ from that of a conventional IVUS catheter. Therefore the potential adverse events associated with the IVUS/NIRS in the additional, non-culprit vessels are expected to be similar to those of the culprit and include, at a very low rate (<1%):

- Additional radiation exposure
- Heart arrhythmias
- Cardiac tamoponade
- Injury to the arteries
- Low blood pressure
- Bleeding
- Stroke
- Heart attack
- Death

7.1 UNANTICIPATED ADVERSE DEVICE EFFECT

Unanticipated Adverse Device Effect (UADE): An UADE is any serious adverse effect on health or safety, or any life threatening problem or death caused by, or associated with the device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this IDE; or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of the subjects. (Significant device failure may constitute an adverse event if an undesirable experience occurs). This definition includes any event resulting

from insufficiencies or inadequacies in the instructions for use or the deployment of the device, or any event that is a result of a user error.

All UADEs should be documented on the appropriate Subject CRF documenting time of onset, a complete description of the event, severity, duration, actions taken and event outcome.

7.2 REPORTING SERIOUS ADVERSE EVENTS

The Investigator shall report all Adverse Effects, whether device related or not, to the Sponsor and to the reviewing IRB as soon as possible (per the overseeing IRB's policy), but in no event later than 10 working days after the Investigator first learns of the effect. The Investigator must determine if the adverse event is "serious." The regulatory definition of "serious" is an event that is fatal or life threatening, resulting in a persistent or significant disability, requiring intervention to prevent permanent impartment/ damage, or an event that results in congenital anomaly, malignancy, hospital admission or prolonged hospitalization. Anything the investigator deems to be serious MUST be reported to the Sponsor within one business day from the knowledge and determination of the event.

8 RISK/BENEFIT ANALYSIS

8.1 ANTICIPATED ADVERSE EFFECTS/ POTENTIAL RISKS FOR 2-3 VESSEL TVC SCANNING

The IVUS-NIRS TVC catheter is designed to function as a conventional, rotating core, IVUS catheter which has an excellent safety record. Experience with NIRS in over 5,000 patients has shown that the TVC catheter safety profile does not differ from that of a conventional IVUS catheter. Therefore the potential adverse events associated with the IVUS/NIRS in the additional, non-culprit vessels are expected to be similar to those of the culprit and include, at a very low rate (<1%):

- Additional radiation exposure
- Heart arrhythmias
- Cardiac tamoponade
- Injury to the arteries
- Low blood pressure
- Bleeding
- Stroke
- Heart attack
- Death

8.2 POTENTIAL BENEFITS

A potential benefit of successful completion of this study for a patient with coronary artery disease is the demonstration that the NIRS-IVUS instrument can identify plaques that are at high-risk for rupture leading to a coronary event. If this phase of the study is positive, the next step will be to test novel local and/or systemic treatments to prevent the development of coronary events.

9 EXPENSE/REIMBURSEMENT TO SUBJECT

Subjects will not be reimbursed for participation.

10 MONITORING COMMITTEES

10.1 DATA SAFETY MONITORING COMMITTEE

The Data Safety Monitoring Committee (DSMC) will consist of one cardiologist and one bio-statistician with the remaining members to be announced. The purpose of the committee during the course of the trial will be to review accumulating safety data, to monitor the hazard ratio with regard to the Endpoints and other trends that would warrant modification or early termination of the trial.

The DSMC may request any data it deems necessary to review. The minimum frequency of DSMC meetings will be twice during the study period and to establish the charter prior to the first data review meeting. The DSMC may call a meeting at any time if there is a reason to believe there may be a safety issue with the study. The DSMC chairperson will notify the sponsor of the meeting conclusions by confidential memo of any needed communication.

Any DSMC recommendations for study modification or termination, because of concerns over patient safety or issues relating to data monitoring or quality control, will be submitted to the sponsor of the trial in writing for consideration and final decision. If the DSMC at any time determines that a potential serious risk exists to patients in this trial, the DSMC chairman will immediately verbally notify the Sponsor, followed by written notification of the concern.

10.2 CLINICAL EVENTS ADJUDICATION COMMITTEE

A Clinical Events Committee (CEC) consisting of at least three members will be established to review and adjudicate all clinical endpoints as defined in the protocol. The CEC will be independent from the study Sponsor. The primary mission of the Committee is to audit and review any major clinical event that occur within the follow up period for the purpose of accurate classification. The Committee will meet on an on-going basis as necessary to assure timely review of the data. Endpoint adjudication will be transmitted to the Data Analysis Center at MedStar for adjustment of the final database as necessary. The CEC will be blinded to all the Index IVUS-NIRS findings throughout the duration of the study.

11 INFORMED CONSENT

All subjects meeting the inclusion and exclusion criteria will be screened by the research staff and asked to give consent by a trained staff member. Subjects will be given ample time to consider participation in the trial.

In compliance with federal regulations governing informed consent, the informed consent form that is given to the subject or authorized representative must be in a language understood by the subject or his/ her legal representative. Prior to participation in the study, each subject must give written informed consent after having the study fully explained to him/her in the language that is most easily understood by the subject. All subjects must be given the opportunity to ask questions and to have those questions answered to his/her satisfaction. All informed consent forms must be approved by the IRB/EC before use and no subject may be consented unless such approval has been granted. All informed consent forms must be written in accordance with the current guidelines as outlined by GCP, ICH, and the Declaration of Helsinki (as applicable).

All informed consent forms must be signed and dated by the person providing explanation of the study and signed and dated by the subject or his/her legal representative prior to participation in this research study. A signed and dated copy of the informed consent form will be given to each subject.

12 ETHICAL CONSIDERATIONS

12.1 DECLARATION OF HELSINKI / GCP/ ICH GUIDELINES

The present trial will be conducted in accordance with:

1. This protocol;
2. International Conference on Harmonization: ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), or equivalent for the United States (Code of Federal Regulations on Good Clinical Practice Title 21 Parts 50, 54, 56, 803, 812, and 814); and
3. The principles that have their origin in the Declaration of Helsinki (if applicable), local laws and regulations.

12.2 INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC)

A copy of the protocol, proposed Informed Consent Forms, all written subject information, and any proposed advertising material must be submitted to the institution's IRB or EC for written approval. No site may initiate study procedures/activities until such IRB or EC approval has been granted in writing. A copy of the written IRB or EC approval of the protocol and Informed Consent Form must be received by the Sponsor of the trial before study supplies are shipped to the investigative site.

The Investigator must submit and, where necessary, obtain IRB or EC approval for all protocol amendments and changes to the Informed Consent Form. The investigator must notify the IRB or EC of protocol violations and UADE or SAEs occurring at the site as required by local regulations.

If any investigator, co-investigator or sub-investigator participating in this study is a member of the IRB or EC approving the study for the site, documentation must be provided by the IRB or EC showing that the investigator did not vote on the approval of the study.

12.3 EMERGENCY ACTIONS

The Sponsor of the trial accepts the right of the investigator to deviate from the protocol in an emergency when necessary to safeguard the life or physical wellbeing of a study subject. The Investigator must notify the sponsor of the trial of any emergency deviations from the protocol as quickly as possible, but in every case less than 24 hours after the emergency.

12.4 AMENDING THE PROTOCOL

This protocol is to be followed exactly and will only be altered by written protocol amendments. If an investigator sees that a protocol amendment is required, the Sponsor for this trial must be notified. Any amendment approved by the Sponsor and Principal Investigator that would affect the benefit/risk ratio or require alteration of the informed consent form must receive approval from the IRB/EC prior to implementation.

13 STUDY ADMINISTRATION

The sponsor of the trial is committed to conducting clinical trials in accordance with the FDA Code of Federal Regulations, Good Clinical Practices, ICH guidelines, and all applicable regulatory requirements.

13.1 PRE-STUDY DOCUMENTATION REQUIREMENTS

The Sponsor of the trial requires specific regulatory documents to be on file prior to shipment of study materials or supplies. The following documents must be provided by the Investigator:

1. Signed and dated Statement of Investigator;
2. Signed and dated site contract;
3. Protocol signature page;
4. Current curriculum vitae with medical license for each Investigator, Co-Investigator or Sub-Investigator;
5. IRB or EC membership list and either a copy of IRB or EC guidelines or a statement that the IRB or EC operates according to GCP and applicable federal regulatory guidelines (Compliance Statement);
6. Written IRB or EC approval of the protocol and informed consent form. The written approval must identify:
    a. The study being approved;
    b. The Investigator who has been given approval;
    c. And must be signed and dated by the chairman or an authorized designee of the IRB.
7. Financial Disclosure from the primary Investigator, Co-Investigators and Sub-Investigators at each site

13.2 RECORD RETENTION

The investigator will retain all regulatory documents pertaining to this study in compliance with ICH/GCP guidelines. This includes all CRFs, essential study documents, and source documentation that supports the data collected on the study subjects. Specifically, documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have lapsed since the formal discontinuation of the clinical investigation. It is the trial sponsor's responsibility to inform the investigator when study documents no longer need to be retained by the investigative site. The investigator must accept responsibility for ensuring that study documents are not damaged or destroyed. If the investigator withdraws his/her responsibility for maintaining study documents for any reason, he/she must transfer custody of the documents to an individual who will accept responsibility for such maintenance. The investigator must notify the sponsor of the trial, in writing, of any change in custody of study documents.

13.3 CRITERIA FOR EARLY TERMINATION OF A STUDY

The Sponsor of the trial retains the right to terminate the study for valid scientific or administrative reasons or reasons related to the protection of subjects. Investigators will be notified in writing in the event of study termination.

13.4 INVESTIGATOR RESPONSIBILITIES

Each investigator is expected to take seriously his or her obligation to conduct the sponsored clinical research trial according to the protocol and in compliance with ICH/GCP guidelines and all relevant local/federal regulations.

14 REFERENCES

1. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733– 43.

2. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Cardiol 2006;47 Suppl 8:C13–8.

3. Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868–874.

4. Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, Virmani R, Muller JE. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. J Am Coll Cardiol. 2007;50:940–949.

5. Kolodgie FD, Burke AP, Farb A, Gold HK, Yuan J, Narula J, Finn AV, Virmani R. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. Curr Opin Cardiol.2001;16:285–292.

6. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 2000;20:1262–1275.

7. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226 –35.

8.Gardner CM, Tan H, Hull EL, et al. Detection of lipid-core coronary plaques in autopsy specimens with a novel catheter-based near infrared spectroscopy system. J Am Coll Cardiol Img 2008;1:638–648.

9. Waxman S, Dixon SR, L'Allier P, et al. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: initial results and exploratory analysis of the SPECTroscopic Assessment of Coronary Lipid (SPECTACL) multicenter study. J Am Coll Cardiol Img 2009;2:858–868.

10.Goldstein JA, Grines C, Fischell T, et al. Coronary embolization following balloon dilation of lipid-core plaques: prospective detection of at-risk lesions by intravascular spectroscopy. J Am Coll Cardiol Img 2009;2:1420–1424.

11. Schultz C, Serruys PW, van der Ent M, et al. First-in-man clinical use of combined nearinfrared spectroscopy and intravascular ultrasound - a potential key to predict distal embolization and no reflow? J Am Coll Cardiol 2010; 56:314.

12. Goldstein JA, Maini B, Dixon SR, et al. Detection of lipid-core plaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. Circ Cardiovasc Interv 2011;4:429–437.

13. Madder RD, Smith JL, Dixon SR, Goldstein JA. Composition of target lesions by nearinfrared spectroscopy in patients with acute coronary syndrome versus stable angina. Circ Cardiovasc Interv 2012;5:55-61.

14. Ryan Madder; Sean Madden; Rishi Puri; Michael Hendricks; Stacie Vanoosterhout; Steve Sum; Annapoorna Kini; Samin Sharma; David Rizik; Emmanouil Brilakis; Kendrick Shunk; James Goldstein; Giora Weisz; Renu Virmani; Stephen Nicholls; Akiko Maehara; Gary Mintz; Gregg Stone; James Muller. Detection by Near-infrared Spectroscopy of Large Lipid-rich plaques at Culprit Sites in Patients with Acute ST-Segment Elevation Myocardial Infarction. TCT meeting-2012

Document History:

Rev	DCR	Date:	Change Description	Change Originator
A	13-490	27NOV13	• Initial Release	P. Shah
B	13-546	30DEC13	• Addition of NIRS Blinding	P. Shah