ProspectIve, Randomized, SingLe-Blind, U.S. MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon

ILLUMENATE Pivotal Post-Approval Study

PROTOCOL

Protocol Number:	D035940
Revision Date:	14 April 2017
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I have reviewed this protocol and agree to adhere to the requirements and responsibilities listed herein. I am trained to the contents of this protocol, percutaneous angioplasty procedures, and the specific use of the devices listed in this protocol. I will ensure that the study is conducted in compliance with the protocol, Instructions for Use, Good Clinical Practices, Declaration of Helsinki and all applicable regulatory requirements.

_____ _____
Site Investigator Signature Date

_____
Site Investigator Printed Name

SUMMARY OF CHANGES

Revision Level	Change Order	Description of Changes
A		Initial Release

PROTOCOL SUMMARY

Device	Stellarex™ 0.035" Over-the-Wire (OTW) Drug-Coated Balloon (DCB) (Stellarex DCB)
Control	Bare Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter (bare balloon catheter))
Study Objective	To continue evaluate the long-term safety and effectiveness of the Stellarex DCB
Study Design	Continued follow-up of premarket ILLUMENATE Pivotal Study subjects
Number of Subjects	300 subjects from the ILLUMENATE Pivotal study. 200 DCB subjects 100 PTA subjects
Number of Sites	43
Primary Effectiveness Endpoint	Patency at 24 months post-procedure. Patency is defined as the absence of target lesion restenosis as determined by duplex ultrasound (Peak Systolic Velocity Ratio (PSVR) ≤ 2.5) and freedom from clinically-driven target lesion revascularization.
Primary Safety Endpoint	Freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 24 months post-procedure.
Secondary Endpoints	• Major adverse event (MAE) rate at 24, 36, 48 and 60 months post-procedure, defined as a composite rate of cardiovascular death, target limb major amputation and clinically-driven target lesion revascularization (TLR). • Rate of clinically-driven target lesion revascularization at 24, 36, 48 and 60 months. • Rate of target lesion revascularization at 24, 36, 48 and 60 months. • Rate of clinically-driven target vessel revascularization at 24 and 36, 48 and 60 months. • Rate of target limb major amputation at 24, 36, 48 and 60 months. • Mortality rate at 24, 36, 48 and 60 months. • Rate of occurrence of arterial thrombosis of the treated segment at 24, 36, 48 and 60 months. • Patency rate at 24 and 36 months, defined as the absence of target lesion restenosis as determined by duplex ultrasound (PSVR ≤ 2.5) and freedom from clinically-driven TLR • Change in ankle-brachial index (ABI) from pre-procedure to 24 and 36 months. • Change in walking impairment questionnaire (WIQ) from pre-procedure to 24 and 36 months. • Change in walking distance from pre-procedure to 24 and 36 months. • Change in Rutherford-Becker classification from pre-procedure to 24 and 36 months. • Change in EQ-5D from pre-procedure to 24 and 36 months.
Follow-Up Schedule	• Office visits will occur at 24 and 36 months post-procedure to review medication compliance, clinical assessments, functional status, adverse events and patency by duplex ultrasound.

	• Telephone contact will occur at 48 and 60 months post-procedure to review medication compliance and adverse events. Office visits are optional for these assessments.
Planned Schedule	• Last subject last contact: 2020

1. STUDY OVERVIEW AND RATIONALE

1.1 Background and Literature Review

Peripheral arterial disease (PAD), atherosclerosis in vessels outside of the heart and brain, is a common ailment affecting an estimated 27 million adults in Europe and North America and is associated with significant morbidity and mortality.[1] Peripheral arterial disease is associated with significant reduction in health-related quality of life, and in extreme cases, the disease can result in debilitating symptoms (including loss of limbs). Total disease prevalence has been estimated at between 3% and 10%, increasing to 15% to 20% in patients over 70 years.[2] Only approximately 25 percent of patients undergo treatment for the disease.[3] Deterioration or progression of PAD occurs in one-third to one-fourth of all patients.[4] One to five percent will eventually require amputation.[4-6]

Peripheral arterial disease is associated with substantial morbidity and reduced health status measures. The most common symptom of PAD is difficulty walking (intermittent claudication); less common is critical limb ischemia (CLI) which includes severe persistent rest pain requiring treatment with analgesics, ulceration or gangrene on the distal extremity. Lower extremity arterial disease can lead to reduced mobility, limb pain, gangrene, and amputation, as well as increased mortality.[2,7,8] Physical function, pain, and general health perception is similar or worse than in patients with congestive heart failure or recent myocardial infarction. In addition, patients with PAD generally also present with cardiovascular disease (CVD), which may explain the increased risk of mortality from myocardial infarction (MI) and stroke,[7,9,10] with mortality rates at five years ranging from 30% to 44%.[11,12]

The superficial femoral artery (SFA) is the most commonly diseased artery in the peripheral (lower limb) vasculature, with PAD presenting as intermittent claudication. Patients with intermittent claudication report increased pain and limitations in physical functioning compared with published norms, which are expected based on the nature of their disease. They also report significant deficits in energy, emotional reactions, sleep, and normal activities of daily living due to emotional stress. These limitations have been reported to occur at a relatively low level of exercise.[4-6]

Available therapies for patients with PAD include: risk factor modification, including diabetes control, smoking cessation, and hyperlipidemia control; exercise therapy; pharmacological therapy; and surgical or endovascular revascularization. Risk factor modification therapy is recommended to improve claudication and decrease the morbidity and mortality associated with the progression of PAD.[2,13] Exercise therapy can produce clinical improvements in walking ability and reductions in claudication pain.[2,13-15] Pharmacological options include antiplatelet and anticoagulant therapies.[16-18] Surgery is typically reserved for patients with critical limb ischemia and is associated with risks such as wound complications, death, MI, infection and leg edema.[18,19] Patency rates at 1 year for surgical revascularization of the lower extremities have been reported to be 40-80%.[20-22]

Multiple published studies report on the short and long-term results of performing percutaneous angioplasty interventions (including PTA without a drug coating) and/or stenting for PAD. Patency rates at 1 year have been reported to range between 29-93%.[23-42] A meta-analysis of PTA to treat SFA lesions up to 15 cm in length reported a 12-month primary patency rate of only 33%.[43] Treatment with bare metal self-expanding stents yields higher but variable 1-year patency rates

that range between 52%[44] and 81%.[45]

Restenosis remains a major limitation of the clinical usefulness of PTA and stenting. Poor long-term results, especially after the treatment of longer lesions in the femoropopliteal region, have been reported.[46-52] Paclitaxel is an antineoplastic drug that has demonstrated sustained inhibition of smooth muscle cell proliferation in several pre-clinical studies.[53-56] Publications related to effectiveness of local administration of paclitaxel on restenosis through use of drug-coated balloons in the femoropopliteal artery have highlighted promising results with reduction of neointimal proliferation in the peripheral arteries.[57-60]

Cassese et al. conducted a systematic meta-analysis of 4 randomized trials comparing paclitaxel drug-coated balloon (DCB) angioplasty to uncoated balloon (PTA) angioplasty.[61] The primary endpoint was target lesion revascularization, with angiographic binary restenosis, late lumen loss, and all-cause mortality as secondary endpoints. The studies in the meta-analysis included THUNDER,[57] FemPac,[58] PACIFIER,[62] and the LEVANT I study.[60] The meta-analysis included 381 patients with a median follow-up time of 10.3 months. The rate of TLRs was significantly lower in the patients treated with DCB (12.2%) in comparison to PTA (27.7%), with an odds ratio of 0.23 (95% confidence interval: 0.13 – 0.40, $p<0.00001$). The authors concluded that DCB therapy has superior antirestenotic efficacy with no evidence of a differential safety profile.

The IN.PACT SFA trial, a multi-center, randomized study comparing the IN.PACT Admiral DCB (n=220) to the uncoated control balloon (n=111) in patients with femoropopliteal PAD, showed significantly higher primary patency for the DCB group (82.2%) vs. control (52.4%; $P<0.001$) at 12 months and at 24 months (78.9% vs. 50.1%; $P<0.001$).[59,63] Clinically-driven TLR rates at 12 months were 2.4% for the DCB group vs. 20.6% for control ($P<0.001$) and at 24 months were 9.1% vs. 28.3% ($P<0.001$), respectively.[59,63] A recent presentation at Vascular Interventional Advances (VIVA) in 2016 showed that the benefits of DCB over PTA were maintained out to 3 years with primary patency of 69.5% vs. 45.1% and CD TLR rates of 15.2% vs. 31.1% for the DCB vs. PTA group.[64]

The Lutonix DCB was also evaluated in a multi-center, randomized trial in comparison to an uncoated control PTA balloon, with 316 DCB subjects and 160 PTA subjects. The results at 12 months showed significantly better primary patency for the DCB group (65.2%) in comparison to the PTA group (52.6%; $p=0.02$), with similar rates of target lesion revascularizations (12.3% DCB vs. 16.8% PTA).[65]

The Stellarex DCB has been studied in several clinical studies. The initial experience included a prospective, multi-center, single arm clinical study performed in Europe, referred to as the ILLUMENATE First-in-Human (FIH) study. The objective of the study was to evaluate the safety and inhibition of restenosis of the Stellarex DCB for treatment of *de novo* or restenotic superficial femoral artery (SFA) or popliteal arteries. The first fifty (50) subjects were treated with pre-dilatation prior to treatment with the Stellarex DCB (Cohort 1) and the second thirty (30) subjects were treated without the pre-dilatation step (Cohort 2).

The results from Cohort 1 (with pre-dilatation) showed that the primary endpoint of LLL at 6 months (mean LLL 0.54±0.97mm; 95% confidence interval: 0.28 to 0.81mm), as assessed by the angiographic core laboratory, was significantly less than the objective performance criterion (1.1mm).[66] The major adverse event (MAE) rate at 6 months, defined as a composite rate of cardiovascular death, index limb amputation, and CD TLR, was 4.0% (95% confidence interval:

0.5 to 13.7%), which was significantly lower than the pre-specified objective performance criterion (30%).[66] The study endpoints were met. The primary patency rate, defined as PSVR ≤ 2.5 without a CD TLR, was 89.5% at 12 months and 80.3% at 24 months (based on the Kaplan-Meier analysis). The freedom from CD TLR Kaplan-Meier rate was 90.0% at 12 months and 85.8% at 24 months.[66] Additionally, there were no amputations or cardiovascular deaths reported through 24 months.

The 2-year results from Cohort 2 (Direct Cohort) were presented at Vascular Interventional Advances (VIVA) in 2015.[67] Twenty-eight subjects with 37 lesions were included in the Cohort 2 analysis; 2 subjects were excluded because they were pre-dilated. The mean lesion length was 6.4cm and calcification was present in 48.6% of lesions. At 6 months, the mean LLL was 0.03mm. The MAE rate was 14.8% at 12 months and 18.5% at 24 months, primarily driven by CD TLRs. There was 1 index limb amputation observed within 6 months in conjunction with lower limb vessel thrombosis in a subject who had a stent placed during the procedure. The primary patency rate (per Kaplan-Meier analysis) was 86.2% at 12 months and 78.2% at 24 months, similar to the rates observed in the pre-dilatation cohort (Cohort 1). The freedom from CD TLR Kaplan-Meier rate was 85.4% at 12 months and 81.7% at 24 months.[67]

The 12-month results from the 2 randomized, controlled trials studying the Stellarex DCB in comparison to PTA control devices have also been presented at scientific meetings. Primary patency at 12 months was 83.9% vs. 60.6% in the ILLUMENATE EU RCT study ($p<0.001$) and 76.3% vs. 57.6% in the ILLUMENATE Pivotal study ($p=0.003$).[68,69] The CD TLR rates were also favourable for the Stellarex DCB in both studies (5.9% vs. 16.7% in the ILLUMENATE EU RCT study and 7.9% vs. 16.8% in the ILLUMENATE Pivotal study).[68,69] The primary safety endpoint, defined as a composite of freedom from device and procedure-related death through 30 days and freedom from target limb major amputation and CD TLR through 12 months, was also superior for the Stellarex DCB in comparison to PTA in both studies (94.1% vs. 83.3% through 395 days in the ILLUMENATE EU RCT study and 92.1% vs. 83.2% through 410 days in the ILLUMENATE Pivotal study [$p=0.001$]).[68,69]

Numerous other drug-coated catheter systems using similar technology to that used in the ILLUMENATE Pivotal Study are currently commercially available. The Bard Lutonix drug-coated balloons and the Medtronic IN.PACT Admiral paclitaxel-coated balloons are commercially available through CE Mark approval and Food and Drug Administration approval. Other CE Marked drug-coated balloons include, but may not be limited to, the Freeway balloon (Eurocor GmbH, Bonn, Germany), the Passeo-18 Lux balloon (Biotronik), the Legflow OTW paclitaxel-coated balloon (Cardionovum GmbH), Advance 18 PTX (Cook Medical), Luminor35 (iVascular), and the Elutax SV (Aachen Resonance GmbH).

2. DESCRIPTION OF THE STELLAREX 0.035 DEVICE AND CONTROL DEVICE

2.1. Study Overview

The ILLUMENATE Pivotal PAS is a continued follow-up study which will include 300 subjects from forty-three (43) sites across the United States and Austria previously enrolled in the ILLUMENATE Pivotal pre-market study to evaluate the Stellarex DCB compared to the PTA control device for the treatment of de-novo or post-PTA occluded/stenotic or reoccluded/restenotic (except for in-stent) SFA and/or popliteal arteries.

2.2. Stellarex™ Device

The Stellarex DCB is a commercially available PTA balloon catheter (EverCross™ 0.035" PTA Balloon Catheter, Medtronic, Plymouth, MN 55441, USA) coated with paclitaxel using a proprietary carrier.

Basic Catheter Specifications

- Guidewire: 0.035"
- Balloon Length: 40/80/120 mm
- Sheath Compatibility: greater than or equal to 6 French
- Balloon Diameter: 4/5/6 mm
- Shaft length: 135 cm

The nominal dose density of paclitaxel on the Stellarex DCB is 2.0 µg/mm^2. The nominal dose of paclitaxel on a specific Stellarex DCB is listed in Table 1.

Table 1: Nominal Paclitaxel Dose (µg) per Catheter Length/Diameter

Balloon Diameter (mm)	Balloon Length (mm)		
	40	**80**	**120**
4	1124 µg	2211 µg	3307 µg
5	1335 µg	2636 µg	3880 µg
6	1619 µg	3174 µg	4721 µg

Indications

The Stellarex 0.035" OTW Drug-coated Angioplasty Balloon is indicated for percutaneous transluminal angioplasty (PTA), after appropriate vessel preparation, of de novo or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6 mm.

2.3. Control Device

The control device is a commercially available PTA balloon catheter (EverCross™ 0.035 PTA Balloon Catheter, Medtronic, Plymouth, MN 55441, USA).

Basic Catheter Specifications

- Guidewire: 0.035"
- Balloon Length: 40/80/120 mm
- Sheath Compatibility: greater to or equal to 6 French
- Balloon Diameter: 4/5/6 mm
- Shaft length: 135 cm

Indications

The EverCross Balloon Catheter is intended to dilate stenosis in the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries, and to treat obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also indicated for stent post-dilation in

the peripheral vasculature. For additional information refer to the EverCross Instructions for Use.

3. STUDY DESIGN

The objective of this continued follow-up of ILLUMENATE Pivotal Study subjects is to demonstrate the long term safety and effectiveness of the Stellarex DCB.

Each enrolled subject will be followed for 5 years (60 months) after treatment. A follow-up office visit will occur at 24 and 36 months. A follow-up telephone contact or an optional office visit will occur at 48 and 60 months.

3.1. Primary Endpoints

Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is patency at 24 months post-procedure. Patency is defined as the absence of target lesion restenosis as determined by duplex ultrasound (Peak Systolic Velocity Ratio (PSVR) ≤ 2.5) and freedom from clinically-driven target lesion revascularization.

Primary Safety Endpoint

The primary safety endpoint for this study is freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 24 months post-procedure.

3.2. Secondary Endpoints

The following endpoints will be also evaluated as secondary endpoints:

- Major adverse event (MAE) rate at 24, 36, 48 and 60 months post-procedure, defined as a composite rate of cardiovascular death, target limb major amputation and clinically-driven target lesion revascularization (TLR).
- Rate of clinically-driven target lesion revascularization at 24, 36, 48 and 60 months.
- Rate of clinically-driven target vessel revascularization at 24 and 36, 48 and 60 months.
- Rate of target limb major amputation at 24, 36, 48 and 60 months.
- Mortality rate at 24, 36, 48 and 60 months.
- Rate of occurrence of arterial thrombosis of the treated segment at 24, 36, 48 and 60 months.
- Patency rate at 24 and 36 months, defined as the absence of target lesion restenosis as determined by duplex ultrasound (PSVR ≤ 2.5) and freedom from clinically-driven TLR
- Change in ankle-brachial index (ABI) from pre-procedure to 24 and 36 months.
- Change in walking impairment questionnaire (WIQ) from pre-procedure to 24 and 36 months.
- Change in walking distance from pre-procedure to 24 and 36 months.
- Change in Rutherford-Becker classification from pre-procedure to 24 and 36 months.
- Change in EQ-5D from pre-procedure to 24 and 36 months.

3.3. Study Population

Subjects included in this study will be comprised of subjects enrolled in the ILLUMENATE Pivotal pre-market study. Three hundred subjects with documented symptomatic superficial femoral and/or

popliteal artery disease who were eligible to be treated by interventional therapy and met all of the inclusion criteria and none of the exclusion criteria of the Pivotal study were enrolled.

3.4. Ethical Considerations

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization Good Clinical Practices (ICH GCP), 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, 812 and 814, International Organization for Standardization (ISO) 14155 [European Union (EU) only], and other applicable regulatory requirements.

3.5. Subject Discontinuation

Every subject should remain in the trial until completion of the required follow-up period; however, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Whenever possible, the investigator should obtain written documentation from the subject that wishes to withdraw their consent for future follow-up visits and contact. The reason for withdrawal, when it occurs, must be documented in the subject's medical records. Prior to study discontinuation, it is recommended that a final visit occur to assess clinical status, adverse events and current medications. The subject will be followed per the institution's standard of care. Reasons for discontinuation may include, but are not limited to, the following:

- The investigator terminates the subject's participation if discontinuation in the study is deemed medically necessary.
- The subject does not complete the scheduled follow-up but has not 'officially' withdrawn from the trial (e.g. "lost to follow-up"). This does not apply to missed visits.
- The subject develops medical conditions such as the following:
    - Reaction to acute treatment requires alternative treatment or intervention (e.g. allergic reaction to paclitaxel, complication with non-study device) where study objectives cannot be objectively evaluated.
    - Unanticipated hospitalization requiring treatment or therapy conflictive with study objectives and preventing compliance with study requirements.

Site personnel should make all reasonable efforts to locate and communicate with subjects at each contact time point. A minimum of two telephone calls to contact the subject should be recorded in the source documents, including date, time, and initials of site personnel trying to make contact. If these attempts are unsuccessful, a letter should be sent to the subject. If the subject misses two consecutive scheduled contact time points and the above mentioned attempts at communicating with the subject are attempted but unsuccessful, the subject will be considered "lost to follow-up".

A study exit form must be completed when a) the subject successfully completes the study, b) the subject is considered "lost to follow-up" (per the above criteria), c) the subject withdraws from the study d) the investigator withdraws the subject from the study or e) the subject dies. In each case of subject discontinuation, the Sponsor must be notified of the reason for subject discontinuation. The site will provide this information on the case report form (CRF) and in the source documents. Withdrawn subjects will not be replaced in this trial.

3.6. Early Termination of the Clinical Trial

Spectranetics, the trial Sponsor, reserves the right to discontinue the clinical study at any stage, with suitable written notice to the investigator. The investigator may also discontinue participation in the clinical trial with suitable written notice to the Sponsor.

Notification of suspension or termination will occur no later than five (5) business days after the sponsor makes the determination. In the event of study suspension or termination, the sponsor will send a report outlining the circumstances to the IRBs/ECs and all investigators. A suspended or terminated study may not be re-initiated without approval of the reviewing IRB/EC (where applicable). The investigator should follow subjects as standard of care at the institution.

4. CONDUCT OF THE STUDY

4.1. Subject Medication Management

Subjects are required to be treated with ASA for the duration of the trial, (5 years) unless there is a contraindication to such. Recommended ASA dose is 81 mg daily.

The medication history will be updated as needed to include modifications to the anticoagulants, anti-platelets and statins following the procedure.

4.2. Subject Follow-up

Subjects will be followed at pre-determined time points during the study as summarized in the Schedule of Events in Table 2.

Table 2: Schedule of Events: 24 Months through 60 Months

EVENT	24 Months	36 Months	48 Months	60 Months	Unscheduled*	Re-intervention*
Visit Window	730 ± 45 days	1095 ± 45 days	1460 ± 45 days	1825 ± 45 days	As clinically indicated	As clinically indicated
Visit Type	Office	Office	Phone	Phone	Office	Office
Anticoagulants, Antiplatelets, and Statins	✓	✓	✓	✓	✓	✓
Peripheral Angiogram with Runoff						✓
Duplex Ultrasound Examination	✓	✓			✓	✓
Ankle-Brachial Index	✓	✓			✓	✓
Rutherford-Becker Classification	✓	✓			✓	✓
6-Minute Walking Test	✓	✓				
WIQ	✓	✓			✓	✓
EQ-5D	✓	✓			✓	✓
Health Economic Evaluation	✓	✓	✓	✓	✓	✓
Adverse Events	✓	✓	✓	✓	✓	✓

* *NOTE: While an attempt should be made to collect all non-invasive testing at unscheduled visits or re-interventions, a protocol deviation will not be required if all assessments are not completed. For re-interventions, the angiogram and duplex ultrasound should be completed per the respective core laboratory guidelines.*

5. ADVERSE EVENTS

5.1. Adverse Events

At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purposes of this protocol, an adverse event is any untoward medical occurrence in a study subject which occurs or worsens, whether or not considered related to the study device, study procedures, or study requirements.

Serious adverse events (SAEs) are any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires medical/surgical intervention to prevent life-threatening illness or injury or to prevent permanent impairment of a body structure or function, or is a congenital anomaly/birth defect. Emergency room visits lasting less than 24 hours are not

considered SAEs.

Major adverse events (MAEs) include cardiovascular death, target limb major amputation and clinically-driven target lesion revascularizations. Refer to Appendix C for definitions.

Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning. Additionally, subjects should be instructed to contact the investigator if any SAEs occur between study visits. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE CRF. The sponsor may request AE source documentation from the site to facilitate adjudication of AEs.

Adverse event reporting began when the subject was enrolled in the ILLUMENATE Pivotal study. All SAEs and MAEs are to be captured and reported to the sponsor via the AE CRF within 10 business days of the investigator learning of the event in the US, and within 3 business days in the EU. The site should not wait for full details to make the initial report to the sponsor. The site is responsible for reporting AEs to the IRB/EC according to the board's reporting guidelines.

For each AE the following should be documented on the appropriate CRF: start date of the event, treatment, resolution, assessment of seriousness, relationship to the study device and relationship to the study procedure. Adverse events should be followed to resolution or stabilization.

Adverse events that are present at the end of a subject's participation in the study should be marked as on-going on the CRF and the subject should receive post-treatment follow-up as appropriate and standard of care at the institution. All adverse events from enrollment in the ILLUMENATE Pivotal study through completion of this post-approval study will be reported.

5.2. Anticipated Adverse Events

An anticipated adverse event is any untoward medical occurrence in a subject whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or Instruction for Use that is identified or worsens during a clinical study.

The following is a list of adverse events that may result from the PTA procedure.

• Abnormal heart rhythms during the procedure	• Hemorrhage
• Abrupt closure	• Hypertension
• Allergic reaction to contrast, concomitant medications	• Hypotension
• Amputation	• Injury to the groin blood vessel
• Aneurysm	• Infection or pain at insertion site
• Arrhythmias (bradycardia & tachycardia)	• Inflammation
• Arterial dissection	• Ischemia
• Arterial perforation or rupture	• Leucopenia
• Artery spasm	• Lymphocele
• Arteriovenous (AV) fistula	• Myocardial Infarction
• Bleeding	• Nausea

• Bypass graft surgery (emergent or non-emergent)	• Pseudoaneurysm
• Chest pain	• Renal failure
• Coagulopathy	• Respiratory failure
• Congestive heart failure	• Restenosis
• Death (cardiovascular or non-cardiovascular related)	• Sepsis
• Discomfort during the procedure	• Seizure
• Distal emboli	• Shock
• Embolism/PTA catheter embolism	• Stroke/cerebrovascular accident (CVA)
• Endocarditis	• Wound complication or wound infection
• Femoral nerve compression with associated neuropathy	• Thrombocytopenia
• Fever	• Thrombosis
• Groin area bruising	• Total occlusion
• Hematoma	• Unstable/stable angina

The following is a list of theoretical adverse events that may result from the addition of paclitaxel to a PTA catheter:

• Abdominal pain	• Leucopenia
• Abnormal liver function test	• Male hypogonadism
• Acne	• Myalgia
• Allergic reaction to paclitaxel	• Pain
• Alopecia	• Peripheral neuropathy
• Anemia	• Pneumonia
• Coagulopathy	• Pyelonephritis
• Edema (non-pulmonary)	• Rash
• Gastrointestinal issues (e.g. diarrhea, vomiting, nausea, pain)	• Renal tubular necrosis
• Hematologic dyscrasia (including neutropenia)	• Sepsis
• Hemolysis	• Thrombocytopenia
• Hypercholesterolemia	• Transfusion
• Hyperlipidemia	• Urinary tract infection
• Hypertension	• Viral, bacterial and fungal infections
• Hypertriglyceridemia	

5.3. Relationship to Study Device

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study device:

Not Related	The event is definitely not associated with device application. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Unlikely	An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
Possible	The temporal sequence between device application and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant or the event abates upon device application completion/removal or the event cannot be reasonably explained by the subject's condition.
Highly Probable	The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application.

5.4. Relationship to Study Procedure

The investigator will use the following definitions to assess the relationship of the adverse event to the original ILLUMENATE Pivotal study procedure:

Not Related	The event is definitely not associated with the study procedure. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Unlikely	An adverse event has little or no temporal relationship to the study procedure and/or a more likely alternative etiology exists.
Possible	The temporal sequence between the study procedure and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant or the event abates upon study procedure completion or the event cannot be reasonably explained by the subject's condition.
Highly Probable	The temporal sequence is relevant and the event abates upon study procedure completion, or reappearance of the event on repeat interventional procedures (re-challenge).

5.5. Unanticipated Adverse Device Effect /Unanticipated Serious Adverse Device Effect

An unanticipated adverse device effect (UADE) is defined as 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 protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

An unanticipated serious adverse device effect is defined as any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

If a complication occurs that the investigator believes may be a potential UADE/USADE, the site should immediately contact the sponsor. All UADEs/USADEs must be documented by the investigator including the date of onset, a complete description of the event, possible reason(s) for the event, duration, actions taken and outcome and submitted to the sponsor as soon as possible. Reporting of UADEs in the US by the investigator must be no more than 10 business days after the investigator learns of the effect. Reporting of USADEs in the EU by the investigator must be within 3 business days. Copies of all supporting documents should be submitted concurrently with the appropriate CRF.

The investigator will submit to the reviewing IRB a report of any UADE that occurs as soon as possible, but no more than 10 business days after the investigator learns of the effect, or sooner if required by the board's reporting guidelines. USADEs should be reported as soon as possible after the event or being informed about the event to the EC.

A report from the sponsor will be submitted to the Food and Drug Administration (FDA) and to all reviewing IRB/ECs and participating investigators within 10 business days after the sponsor first receives notice of the effect.

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

Risk Assessment

In conjunction with the National Principal Investigator(s) and/or, if need be, the Clinical Event Committee and/or Data Safety Monitoring Board (Section 10.2) the sponsor shall decide whether, as a result of an UADE/USADE, the safety of study participants is at risk, or whether continuation of the trial is in jeopardy.

Corrective Measures

If any situation potentially jeopardizing the safety of subjects, users or third persons arise during a clinical trial or approved performance evaluation, then the sponsor and those persons carrying out the clinical trial or the performance evaluation shall immediately take all of the essential safety measures in order to protect subjects, users or third persons from direct or indirect danger.

6. STATISTICAL DESIGN AND ANALYSIS

6.1. Statistical Overview of the Trial

The statistical design of this study is that of a single-blind randomized controlled trial in which there are two co-primary endpoints. The endpoints and their corresponding statistical hypotheses are:

- Non-inferior Safety: Freedom from device and procedure related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven

target lesion revascularization through 24 months post-procedure.

- H_0: $\pi_{DCB} \leq \pi_{PTA} - \delta$
- H_1: $\pi_{DCB} > \pi_{PTA} - \delta$ where π is the population proportion for the corresponding treatment group and δ is the non-inferiority margin.

- Superior Effectiveness: Patency at 24 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from target lesion revascularization.
  - H_0: $\pi_{DCB} \leq \pi_{PTA}$
  - H_1: $\pi_{DCB} > \pi_{PTA}$

The analysis populations are Intention-to-Treat (ITT) and Per-Protocol (PP); they are fully defined below in the next subsection.

6.2 Analysis Populations

The Intention-to-Treat (ITT) population will be comprised of all subjects who successfully completed the preliminary qualification procedures and were subsequently randomized to receive either the Stellarex DCB or the PTA control device.

The Per-Protocol (PP) population will consist of ITT subjects who had no bail-out stenting and no major protocol deviations. The data for each subject will be reviewed by the blinded angiographic core laboratory. All trial endpoints will be analyzed using both the Intention-to-Treat and Per-Protocol populations, with the ITT analysis *a priori* designated as primary.

6.3 Sample Size Justification

Statistical sample size estimation for the two co-primary endpoints are as follows:

Effectiveness:

- Superiority design
- 2:1 treatment assignment ratio
- 80% power
- 1-tailed alpha = 0.025
- Patency proportions: PTA = 47%, representing a reduction of approximately 10% in the PTA group from 12 months, and a difference between groups of 19% (approximately the observed difference between groups in patency at 12 months)
- Therefore N = 236 subjects (= 157 + 79)

Safety:

- Non-inferiority design
- 2:1 randomization ratio
- 80% power
- 1-tailed 0.025
- Non-inferiority margin = 10%

- Success proportions: PTA success rate = 73%, representing a reduction of 10% in the PTA group from month 12, and a difference between groups in favor of DCB of 7% (as compared to an observed difference of 8.9% at month 12)
- Therefore N' = 206 subjects (=137 + 69)

The enrolled sample size of 300 will be sufficient to achieve 80% power for the primary efficacy and safety objectives. It is expected that no more than 20% of subjects will not be evaluable for the primary endpoints (due to early withdrawals, missing data or non-diagnostic/non-evaluable DUS assessment) providing an expected observed sample size of 240. However, all subjects will be included in the analysis as multiple imputation, and clinical imputation for patency, will be employed for subjects with missing endpoint data.

The non-inferiority margin has been increased from 5% for the 12 month endpoint in the Pivotal study to 10% for the PAS endpoint at 24 months. The reason for the increase to the more conventional 10% margin is because an assumption of a 20% difference, the original assumption for the 12 month endpoint, between groups at 24 months is not reasonable given the 12 month results of 92.1% vs. 83.2%.

6.4 Statistical Analyses

General Statistical Considerations

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Continuous variables that are recorded using approximate values (e.g., < or >) will be replaced by the closest exact value for the calculation of summary statistics. Categorical variables will be summarized using frequency counts and percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

A statistical analysis plan (SAP) accompanies this protocol and should be referred to for further information on intended statistical methods; the SAP will be finalized and approved prior to study database lock. The SAP will detail the analytical methodology and assumptions beyond those presented below.

Analyses of Primary Endpoint

Both co-primary endpoints are binary in nature and as such will be summarized as success (or failure) counts, percentages, and Clopper-Pearson 95% confidence intervals. Superiority in effectiveness will be tested using chi-square contingency table methods, corrected for continuity. In the unlikely event that Cochran's Rule is violated, then Fisher's Exact tests will be employed. The primary analysis of the primary endpoints will employ multiple imputation on the ITT cohort to replace missing values. Details of the imputation model are provided in the SAP.

Non-inferiority of safety event rates will employ Farrington-Manning non-inferiority exact tests. Secondary analyses of the primary endpoints, including Kaplan-Meier methods and sensitivity analyses such as use of all TLR in endpoints defined with clinically-driven TLR will be performed and are detailed in the SAP.

Analysis of Secondary Endpoints

All secondary endpoints will be analyzed descriptively without hypothesis-testing.

For binary variables such as MAE or technical success, counts, percentages and exact 95% confidence intervals using Clopper-Pearson's method will be calculated. For continuous variables, means, standard deviations and 95% confidence intervals will be calculated.

Protection Against False Discovery

Insofar as this study is not deemed a success unless both co-primary endpoints (safety and effectiveness) are met, the probability that the trial falsely succeeds purely due to chance is related to the product of the individual endpoint α-levels. Since the endpoints are effectively independent, the probability that both endpoints are met purely by chance is less than 1 out of 1000.

6.5 Blinding

Blinding is critical to the integrity of this clinical trial. Blinding of the treating physician is not possible due to the differences between the investigational and control devices. For the duration of the trial the subject and the core laboratories will be blinded.

In the event of a medical emergency, UADE, or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's health management, the treating physician may act in accordance with knowledge of the actual randomized treatment assignment of the subject.

The need to act on knowledge of the treatment assignment must first be discussed with the sponsor.

Should the trial be suspended or pre-maturely terminated, the sponsor will provide instructions regarding the release of the randomized treatment assignment.

7. RISK ASSESSMENT

7.1. Potential Risks from Peripheral Catheterization, Stenting and PTA

It is expected that risks associated with this study to be not significantly different than those with the standard interventional procedure for SFA disease. The list of adverse events that may result from peripheral intervention includes but is not limited to: abrupt closure, acute myocardial infarction, allergic reaction to contrast, amputation, aneurysm, arterial perforation, arterial rupture, arteriovenous fistula, atrial arrhythmias (including bradycardia and tachycardia), bleeding complications that may require transfusions, artery spasm, stent embolism, peripheral artery or catheter thrombosis or embolism, chest pain, coagulopathy, congestive heart failure, death, drug reactions to antiplatelet agents/contrast medium, discomfort, emergency or non-emergent bypass graft surgery, distal emboli (air, tissue or thrombotic), fever, hypotension, hypertension, infection and pain at insertion site, injury to the peripheral artery, ischemia, leucopenia, lymphocele, nausea and vomiting, pseudoaneurysm, restenosis of the treated segment of the artery, sepsis, seizure, stroke/cerebrovascular accident (CVA), thrombocytopenia, total occlusion of the peripheral artery, unstable or stable angina pectoris, vascular complications including entry site that may require vessel repair, ventricular arrhythmias including ventricular fibrillation, ventricular tachycardia, wound complication or wound infection, renal failure, urinary tract infection and arterial dissection.

7.2. Potential Risks from Paclitaxel Coating

Local vessel toxicity from the paclitaxel coating includes the possibility of thrombosis and aneurysm formation. Certain side effects and discomforts have been reported in subjects that have received paclitaxel in intravenous (IV) form as part of chemotherapy treatment. These subjects may have other comorbid conditions and/or have received concomitant medications that may also have contributed to the reported side effects. In the IV setting, the dose is delivered throughout the body and in doses hundreds of times higher than the total amount present on the CVI Paclitaxel-coated PTA Catheter used in this clinical study. The side effects reported by the chemotherapy subjects include allergic/immunologic reactions, alopecia, anemia, blood product transfusion, gastro-intestinal symptoms, hematologic dyscrasia (including leukopenia, neutropenia, and thrombocytopenia), hepatic enzyme changes, histologic changes in vessel wall, cellular damage or necrosis, myalgia/arthralgia and peripheral neuropathy. It is unlikely with the total dosage on the CVI Paclitaxel-coated PTA Catheter and the targeted vessel delivery of the paclitaxel that the side effects associated with IV high dose chemotherapy would occur.

7.3. Risk Management Procedure

The study will be conducted by skilled and trained investigators relative to interventional procedures. The research team at each clinical site will undergo training prior to initiation of the study.

Subjects will be monitored closely throughout the study duration. Subjects will be evaluated at pre-determined time points to assess their clinical condition. The subject's medication regimen will be in line with standard of care requirements for peripheral interventional procedures.

7.4. Potential Benefits

The local application of anti-proliferative drugs (e.g., sirolimus, zotarolimus, everolimus, and paclitaxel) for prevention of restenosis in coronary arteries via a stent delivery system has shown that these therapies successfully inhibit or reduce restenosis.[70-81] This has reduced the need for subjects with coronary artery disease to undergo repeat percutaneous and surgical revascularizations.

The success of drug-eluting stents in the coronary arteries triggered an increased interest in using drug-eluting or drug-coated therapies in other vasculatures. Neointimal hyperplasia remains one of the major stumbling blocks of all endoluminal therapies, particularly in the small caliber peripheral vessels and long diseased segments.[50,52] To date, most trials involving drug-coated or drug-eluting stents have not shown reduced restenosis rates in the superficial femoral or proximal popliteal arteries.

Preliminary data suggest that drug-coated balloons using paclitaxel reduce restenosis and late lumen loss in the superficial femoral and proximal popliteal arteries when compared to PTA with standard balloon catheters.[57,58] Therefore, drug-coated balloons may have more advantages than angioplasty alone, especially in terms of controlling neointimal hyperplasia and lowering restenosis rates.

8. DATA HANDLING, RECORD KEEPING AND REPORTING

8.1. Case Report Form (CRF) Completion

All required data will be accurately recorded by authorized personnel on standard CRFs which will be provided by the Sponsor. CRFs should be completed within 10 business days of a completed

study visit.

8.2. Source Documentation

Source documentation is defined as all information necessary for the reconstruction and evaluation of the clinical investigation. Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the CRFs. Investigators will maintain all records pertaining to this study as mandated by the hospital requirements and national laws and regulations (e.g. informed consent evidence; nurse notes; hospital charts; correspondence with the sponsor, regulatory authorities or other physicians).

8.3. Reports

A report will be created after the primary endpoint has been analyzed and a final report on the study will be completed at the end of the study. Interim reports may be compiled per regulatory requirements.

9. REGULATORY REQUIREMENTS

This study will be conducted in compliance with the protocol approved by study sites' respective Institutional Review Boards (IRB)/Ethics Committees (ECs) and according to the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (ICH GCP), Title 21 of the Code of Federal Regulations (CFR) Parts 50, 54, 56, 812, and 814, and other applicable regulatory requirements. No planned deviations from the protocol will be implemented without prior review and approval of the sponsor then submitted to IRB/EC pursuant to IRB/EC guidelines. In such cases, the deviation will be reported to the IRB/EC as soon as possible.

9.1. Investigator's Responsibility

The investigator must read and understand the protocol and must sign and complete an investigator agreement form. The investigator agreement form documents the investigator's agreement to all conditions of the protocol and an agreement to conduct the study accordingly.

Additional requirements must be met by the investigator and participating institution, such as compliance with the protocol and protocol amendments, investigator requirements, institutional requirements, subject informed consent, use of information and publication, and reporting requirements.

9.2. Compliance with Protocol and Protocol Amendments

A protocol deviation is defined as any divergence from the study protocol. The investigator is responsible for promptly reporting protocol deviations to their IRB/EC per IRB/EC policy and to the sponsor. The sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety and determine if additional reports or actions are required. Additional action may include site re-training, removal of the devices, and/or site termination.

The investigator will not implement any changes to the protocol without first obtaining a written agreement from the sponsor and documented approval from the IRB/EC, except in the event of an immediate hazard to the subject. The investigator will report the deviation in accordance with the applicable regulations.

9.3. Investigator Requirements

All investigators were approved by the sponsor as part of the ILLUMENATE Pivotal study and remain in good standing with the following required documentation

- Signed investigator's agreement
- Current curriculum vitae
- Financial disclosure form
- IRB/EC approval of the investigator

Investigators must allow the Sponsor or representatives of the Sponsor to visit the site to periodically assess the data quality and study integrity. On site, the Sponsor or representatives will review study records in comparison with source documents, discuss the conduct of the study and verify that the facilities remain acceptable. In addition the study may be evaluated by government inspectors who must be allowed access to CRFs, source documents and other study files.

The investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor.

The investigator should retain essential documents at least two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator must contact the sponsor prior to disposal of study records.

If the investigator withdraws from the study, the responsibility for follow-up and maintaining the study records must be transferred to a responsible party (such as another study investigator). Notice of transfer must be provided in writing by the investigator to the sponsor, FDA/CA and IRB/EC no later than 10 business days after the transfer occurs.

9.4. Institutional Requirements

The investigator and institution are required to submit the following documentation..

- IRB/EC approved informed consent form
- IRB/EC approval of the protocol
- Fully executed clinical study agreement

Any additional requirements imposed by the IRB/EC or regulatory authorities concerning the trial shall be followed. The investigation may not start at the institution until favorable IRB and/or regulatory approval has been obtained.

9.5. Subject Informed Consent

Study subjects were required to provide written informed consent using an IRB-/EC-approved informed consent form as part of the ILLUMENATE Pivotal study. No additional follow-up requirements or testing is required as part of this post-approval study.

9.6. Use of Information and Publication

All information and data generated in association with this study will be held in strict confidence until the study completion. The investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the sponsor.

At the conclusion of each follow-up time point and the entire study, an abstract reporting the primary results may be prepared and presented in an appropriate international forum. A manuscript may also be prepared for publication in a scientific journal. The data and results from the study are the sole property of the sponsor. The sponsor shall have the right to access and use all data and results generated during the study. The sponsor acknowledges that the Principal Investigator(s) might desire to publish a multi-center publication regarding the trial results. The sponsor must receive any proposed publication and/or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the sponsor in compliance with the sponsor's publication policy set forth in the clinical study agreement or investigator agreement.

9.7. Reporting Requirements

Reporting requirements for the investigator are listed in Table 4. Included are information regarding to whom this information is to be sent, and the frequency and time constraints around submissions. If applicable laws, regulations, or IRB/EC requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 2: Site Responsibilities for Submitting Data and Reports

Type of Report	Investigator Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Adverse Events	Sponsor	Adverse events are collected at the time of the procedure and follow-up visits and must be reported to the sponsor as soon as possible.
Serious Adverse Events	Sponsor and IRB/EC/CA	For US: ASAP, but to sponsor within 10 business days of the investigator learning of the event. To IRB according to board guidelines. For EU: ASAP, but to sponsor within 3 business days of the investigator learning of the event. To IRB/EC according to board guidelines. Submission to CA is done by the sponsor as soon as possible.
Unanticipated Adverse Device Effects	Sponsor and IRB/EC	ASAP, but to sponsor within 10 business days of the investigator learning of the effect. To IRB/EC according to board guidelines.
Withdrawal of IRB/EC Approval or other action on part of the IRB/EC that affects the study	Sponsor	Within 5 business days of IRB/EC decision.
Progress Reports (US Only)	Sponsor and IRB/EC	Every 6 months for the first two years and then at intervals dictated by the IRB/EC, but no less than yearly.
Protocol Deviations	Sponsor and IRB/EC	ASAP to sponsor. To IRB/EC according to board guidelines.

Type of Report	Investigator Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Final Report	Sponsor and IRB/EC	For US: To sponsor within 3 months after termination or completion of study or investigator's participation. For EU: To sponsor within 6 months after termination or completion of study or investigator's participation. To IRB/EC according to board guidelines.
Other	IRB/EC/CA, FDA	Upon request to provide accurate, complete, and current information about any aspect of the study.

10. SPONSOR RESPONSIBILITIES COMPLIANCE/QUALITY ASSURANCE

10.1. Role of Sponsor

As the study sponsor, Spectranetics has the overall responsibility for the conduct of the study, including assurance that the study satisfies regulatory requirements.

General Duties

It is the sponsor's responsibility to ensure that the study is conducted according to the ethical principles that have their origin in the Declaration of Helsinki and consistent with ICH GCP, 21 CFR Parts 50, 54, 56 and 812, International Organization for Standardization (ISO) 14155 [European Union (EU) only] and other applicable regulatory requirements, the study protocol, or any conditions of approval imposed by the IRB/CA/EC or regulatory authorities. Additionally, the sponsor will ensure proper clinical site monitoring is conducted.

Training of Investigator and Site Personnel and Monitoring

The training of the investigator, and appropriate clinical site personnel will be the responsibility of the sponsor and Principal Investigator, or designee, and may be conducted during an investigator meeting, a site initiation visit, or other appropriate training sessions.

Periodic monitoring visits will be conducted frequently enough to ensure that all clinical subject data are properly documented and that the study is properly conducted.

Documentation

The sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents:

- Records of any UADEs reported to the sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- The final report of the clinical investigation

10.2. Committees

Clinical Events Committee

The Clinical Events Committee (CEC) is made up of interventional radiologists, interventional cardiologists or vascular surgeons who are not participants in the study. The CEC is charged

with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the protocol.

At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the CEC will be blinded to the primary results of the trial during the period of primary endpoint data collection.

The CEC will meet regularly to review and adjudicate all clinical events. The committee will review and rule on all deaths that occur throughout the trial. The committee will also review and rule on patency when there are two modalities of images available (ultrasound and angiographic) and they are in conflict with each other.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will consist of at least 5 members with 3 members representing a quorum. Membership will include a biostatistician and independent representatives in relevant fields of clinical expertise, including but not limited to, physicians with one of the following specialties: interventional cardiology, vascular surgery, or interventional radiology. DSMB members will be not part of the study or committees related to the study. The DSMB will advise the sponsor regarding the continuing safety of trial subjects, including those to be recruited, as well as the continuing validity and scientific merit of the trial.

11. TRIAL TERMINATION

The sponsor and Steering Committee will monitor the progression of the study. If warranted, the study may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population.

Notification of suspension or termination will occur no later than five (5) business days after sponsor makes the determination. In the event of study suspension or termination, the sponsor will send a report outlining the circumstances to the IRBs/ECs and all investigators. A suspended or terminated study may not be reinitiated without approval of the reviewing IRB/EC (where applicable). The investigator should follow any subjects as standard of care at the institution.

The sponsor has the right to terminate the trial at any time for any reason.

12. APPENDICES

- Appendix A: Bibliographical References
- Appendix B: Helsinki Declaration
- Appendix C: Trial Abbreviations and Definitions
- Appendix D: Rutherford-Becker Classification Guidelines
- Appendix E: ABI Guidelines
- Appendix F: WIQ Guidelines
- Appendix G: 6 Minute Walking Test Instructions
- Appendix H: EQ-5D Instructions
- Appendix I: Investigator Responsibilities

Appendix A: Bibliographical References

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WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

- Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
- 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
- 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and

therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee,

especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified

individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Trial Abbreviations

ABI	Ankle-Brachial Index
AE	Adverse Event
ADE	Adverse Device Effect
ASA	Acetylsalicylic Acid
ASAP	As Soon As Possible
AV	Arteriovenous
BBC	Bare balloon catheter
BMI	Body Mass Index
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Clinically Indicated or Confidence Interval
CLI	Critical Limb Ischemia
CMP	Complete Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVI	CV Ingenuity
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
EC	Ethics Committee
EOB	Explanation of Benefits
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	Identification
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IV	Intravenous
LLL	Late Lumen Loss
MAE	Major Adverse Event
MEC	Medical Ethics Committee
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
MR	Magnetic Resonance
OTC	Over-the-counter
O.U.S.	Outside the United States
PAD	Peripheral Artery Disease
PI	Principal Investigator/Primary Investigator
PP	Per Protocol
PSVR	Peak Systolic Velocity Ratio
PT	Prothrombin Time

PTA	Percutaneous Transluminal Angioplasty
QA	Quantitative Angiography
QALY	Quality-adjusted Life Year
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SFA	Superficial Femoral Artery
TLR	Target Lesion Revascularization
TPG	Translesional Pressure Gradient
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
U.S.	United States
WIQ	Walking Impairment Questionnaire

Trial Definitions

Abrupt Closure

Vessel occlusion at the site of treatment within 24 hours after successful index procedure.

Acute Success

Acute success is classified according to the following definitions:

Clinical Success

Clinical success (per subject) is defined as technical success without the occurrence of major adverse events during the procedure.

Lesion Success

Lesion success is defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50% (as determined by the angiographic core laboratory), using any device after wire passage through the lesion.

Technical Success

Technical success is defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50% (as determined by the angiographic core laboratory), using the CVI Paclitaxel-coated Percutaneous Transluminal Angioplasty Balloon Catheter or bare balloon catheter without a device malfunction after wire passage through the lesion. Pre and post-dilatation of the lesion are considered part of assigned device treatment.

Adjunctive Treatment

A procedure performed after treatment with the protocol-defined treatment

Adverse Events

Adverse Event (US)	An adverse event is any untoward medical occurrence in a study subject which occurs or worsens, whether or not considered related to the study device, study procedures, or study requirements.
Adverse Event (OUS)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Serious Adverse Event (US)	Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires medical/surgical intervention to prevent life-threatening illness or injury or to prevent permanent impairment of a body structure or function, or is a congenital anomaly/birth defect. Emergency room visits lasting less than 24 hours are not considered SAEs. Note: For purposes of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions do not need to be reported as an adverse event or a SAE in the CRF unless there is an increase in severity or frequency during the course of the study. If a procedure is planned prior to enrollment and it is documented in the medical record as planned then an AE or a SAE does not need to be reported in the eCRF.
Serious Adverse Event (OUS)	An adverse event that a) led to a death or b) led to a serious deterioration in the health of the subject that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or

	3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life –threatening illness or injury or permanent impairment to a body structure or body function. c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (see definition above).
Unanticipated Serious Adverse Device Effect (USADE)	Any serious device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Amputation

The removal of a body extremity by surgery.

A minor amputation will be defined as below the ankle; and a major amputation will be defined above the ankle**.**

Aneurysm

A localized, pathological, blood-filled dilatation of a blood vessel caused by a weakening of the vessel wall.

Angina Pectoris

Braunwald Classification of Unstable Angina:

New onset of severe or accelerated angina. Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Canadian Cardiovascular Society (CCS) Classification of Stable Angina:

Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

Ankle Brachial Index (ABI)

The ratio of the highest ankle systolic pressure to the highest brachial systolic pressure.

Anticipated Adverse Event

Any undesirable health related experience occurring to a subject whether or not considered related to the investigational device or drug regimen prescribed as part of the protocol that is predefined in the protocol and/or Instructions for Use that occurs or worsens during a clinical study.

Arterial Inflow

For a lesion in the superficial femoral artery (femoro-popliteal level) inflow refers to the aorto-iliac level. Good inflow implies that vessels proximal to a target treatment site are free of hemodynamically significant lesion stenosis (≥ 50% stenosis).

Arterial Outflow

For a lesion in the superficial femoral artery (femoro-popliteal level) outflow refers to combined levels distal to the lesion, including the following arteries: distal popliteal,

tibioperoneal trunk, anterior tibial, posterior tibial, peroneal, dorsalis pedis, plantar and pedal. Good outflow implies that the distal popliteal, tibioperoneal trunk and at least one of the infrapopliteal arteries (anterior tibial, posterior tibial, peroneal) is free of hemodynamically significant lesion stenosis (≥ 50% stenosis) and that there is in-line flow into the foot.

Arterial Dissection

Intimal disruption of the vessel wall with or without medial or adventitial contrast staining.

Dissection Grades

National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System: (0, A, B, C, D, E, F)

- 0: No dissection.
- A: Minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff.
- B: Luminal flap that is radiolucent and that runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff.
- C: Contrast appears outside of the vessel lumen as an "extra-luminal cap". The staining appears even after contrast clears the lumen.
- D: Spiral radiolucent luminal filling defects. Often persistent staining after contrast clears from the vessel.
- E: New and persistent filling defects in the vessel lumen.
- F: Lesions that progress to impaired flow or total occlusion.

Arterial Perforation

Identifiable by extravasation of contrast media outside the arterial adventitial space.

Arterial Rupture

Large transmural disruption of a vessel with gross extravasation and hemorrhage.

Artery Spasm

A sudden, brief tightening of a blood vessel.

Bleeding

Blood loss resulting from the percutaneous interventional procedure or adjunctive drug therapy that may require transfusion of blood products.

Cerebrovascular Accident (CVA) or Stroke

Neurological dysfunction caused by a brain disturbance or ischemia, with clinical symptoms lasting >24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms.

Compressible Artery[1]

An artery without significant calcification that can be evaluated by duplex ultrasound or an artery that results in an ABI value < 1.3.

Death

The termination of life. When possible, death will be classified according to underlying cause. Death within 30-days of the study procedure will be classified as procedure related unless demonstrated otherwise.

Cardiovascular death:

Any death due to proximate cardiac cause (e.g., myocardial infarction (MI), low-output failure, fatal arrhythmia), unwitnessed death, or death of unknown cause.

Device Malfunction

A device malfunction is any case when the device does not perform in its intended function when used in accordance to the Instructions for Use.

Discharge

The time point at which the subject was released from the admitting hospital or transferred to another facility.

Embolism

Obstruction of a blood vessel by a foreign substance (air, plaque, debris) or a blood clot.

Enrollment

The patient will be considered enrolled into the study upon the completion of all the following:

- A signed patient informed consent;
- General and angiographic inclusion/exclusion criteria for enrollment has been met;
- Successful treatment of the inflow (iliac) artery without complication, if applicable;
- Target lesion is successfully crossed by the guidewire;
- The pre-dilation has been completed (with a non-study catheter that is at least 1 mm smaller in diameter than the nearest reference vessel diameter) without a flow-limiting (Grade D or greater) dissection, stent placement, or residual stenosis >70%; and
- Randomized treatment has been assigned.

[11] Creager Mark, Victor Dzau, and Joseph Loscalzo, eds. Vascular Medicine: A Companion to Braunwald's Heart Disease. Philadelphia, PA: Saunders Elsevier, 2006.

Fever

An increase in internal body temperature to levels that are above normal (37°C, 98.6°F).

Gastrointestinal (GI) bleeding

Any bleeding that starts in the gastrointestinal tract, which may extend from the mouth to the anus.

Hemorrhage

Bleeding requiring hospitalization, repeat procedure, operation or transfusion.

Hypertension

Increase in systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg.

Hypotension

Fall in systolic blood pressure that requires intravenous treatment with vasopressors or inotropic agents.

Index Procedure

The procedure in which the subject has the study procedure performed or attempted.

Infection

Inflammation caused by bacterial or viral sources, such as, urinary tract infection, puncture site infection, sepsis, endocarditis, and bacteremia from IV site.

Inflammation

An immunologic response to infection or trauma that can result in localized redness, swelling, heat, pain and dysfunction of the organs involved.

Intent-to-Treat (ITT) Population

Subjects who successfully complete the preliminary qualification procedures and are subsequently randomized to receive either the investigational device (CVI Paclitaxel-coated PTA Catheter) or the control device (bare balloon catheter).

Intraluminal thrombus

A blood clot within a vessel.

Invasive Assessment/Procedure

Any assessment, intervention or therapy that penetrates the skin, excluding administration of parenteral fluids or drugs.

Late Lumen Loss (LLL)

Calculated as Minimum Lumen Diameter (MLD) post-procedure – MLD at follow-up. Mean in-lesion Late Loss will also be measured: (Mean In-lesion MLD, post-procedure) – (Mean In-lesion MLD at follow-up).

Major Adverse Event (MAE)

Events including cardiovascular death, target limb major amputation and clinically-driven target lesion revascularization (TLR).

Minimum Lumen Diameter (MLD)

The average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. MLD is visually estimated during angiography by the Investigator and is also measured by the Angiographic Core Lab.

Multilevel Disease

Presence of obstructive lesions at more than one level in the same extremity as the treatment lesion.

Myocardial Infarction[2]

Criteria for acute myocardial infarction:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native

[2] Third universal definition of myocardial infarction. Thygesen K, et al. Eur Heart J. 2012 Oct;33(20):2551-67

coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

National Principal Investigator

A physician-specialist, related to the study, which is responsible for the overall conduct of the trial at all sites in a country.

Occlusion

An obstruction within an artery.

Patency Rate

Patency rate defined as the absence of target lesion restenosis determined by duplex ultrasound peak systolic velocity ratio (PSVR) of ≤ 2.5 and freedom from clinically-driven target lesion revascularization.

Ultrasound evidence will be used first to determine patency.

- Ultrasound images showing a PSVR of ≤ 2.5 will be considered patent by the core laboratory. In the event that the core laboratory cannot determine the PSVR, the core laboratory will make an assessment as to whether or not the lesion is patent, 50-99% stenosed or occluded.
- If ultrasound images are not available at a follow-up or analysis time point, and if an angiogram evaluation is available, the angiogram will be used to determine patency. A result of ≤ 50% residual stenosis will be considered patent.

Patent Run-Off

A vessel starting at the popliteal artery going to the foot presenting with patent flow (hemodynamically insignificant stenosis of < 50%).

Peak Systolic Velocity Ratio

In-lesion duplex ultrasound measurement that measures the peak velocity of blood (cm/second) within a lesion or stented vessel segment divided by the peak velocity of blood (cm/second) proximal to the lesion or stented vessel segment.

Percent Diameter Stenosis

Relative changes that occur in the percent diameter stenosis are provided by the following relationship: % diameter stenosis= (1-[MLD/Reference diameter]) x 100

Per Protocol

ITT subjects who had no bail-out stenting and no major protocol deviations. The data for each subject will be reviewed by the blinded angiographic core laboratory.

Physician-Directed Subject Withdrawal

Withdrawal of a subject from the study at the direction of the Principal Investigator. Reasons for physician-directed subject withdrawal include, but are not exclusive to: the subject is not adhering to the study protocol requirements, the subject has enrolled in another study that conflicts with the ILLUMENATE Pivotal outcomes of interest, or the physician deems it in the best interest for the safety or welfare of the subject to withdraw.

Popliteal Artery

Defined as the vessel located between Hunter's canal and the trifurcation of the anterior tibial, posterior tibial and peroneal arteries.

Pre-Procedure

The time until the procedure begins (before arterial access is obtained).

Protocol Deviation

Any divergence from the Study Protocol.

Principal Investigator (PI)

Physician responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the Study Protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs eCRF indicating documents are accurate and complete.

Reference Vessel Diameter (RVD)

An approximation of the diameter of the vessel at the location of the target lesion. RVD is the average of vessel diameters proximal and distal to the target lesion. It will be estimated or measured by the Investigator and also measured by the angiographic core laboratory.

Renal Failure

Failure of the kidneys to perform essential functions that requires dialysis.

Restenosis

Re-narrowing of the artery following the reduction of a previous narrowing. It is defined as the presence of a PSVR ≥ 2.5 by duplex ultrasound or a hemodynamically significant restenosis ($\geq 50\%$ stenosis), as determined by angiography.

Restenotic Lesion

A lesion in a vessel segment that had undergone a prior percutaneous treatment.

Runoff Vessel

An artery distal to treated vessel, including the popliteal, peroneal tibials and the dorsalis pedis.

Rutherford-Becker Classification Categories

A classification system of clinical categories of chronic limb ischemia ranging from 0 to 6. The categories and clinical descriptions are:

Category	Clinical Description
0	Asymptomatic, no hemodynamically significant occlusive disease
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia
6	Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable

Sepsis

Systemic inflammatory response to infection.

Severe Calcification

Radiopacities noted on both sides of the arterial wall and extending more than one cm of length prior to contrast injection or digital subtraction angiography.

Stenosis

An abnormal narrowing of an artery.

Study/Research Coordinator

Employee at study site who assists Principal Investigator with study activities as delegated by the Principal Investigator, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing and providing eCRFs to the sponsor in a timely manner.

Sub-Investigator(s)

Physician(s) responsible for study activities in coordination with Principal Investigator and in accordance to the Study Protocol.

Successful Pre-Dilation

Pre-dilation (with a non-study catheter that is at least 1 mm smaller in diameter than the nearest reference vessel diameter) has been successfully completed without complications if all of the following apply:

- Residual diameter stenosis ≤ 70%
- No stent placed.
- No flow-limiting (Grade D or greater) dissections

Superficial Femoral Artery (SFA)

The SFA connects to the popliteal artery at the opening of adductor magnus or hunter's canal towards the end of the femur.

Tandem Lesions

Two distinct lesions with 3 cm or less of healthy vessel separating the diseased areas; this total area (diseased segments plus the 3 cm or less of healthy vessel) must be treatable by no more than 2 devices and ≤18 cm in cumulative length.

Target Lesion

A single diseased segment, between 3 cm and 18 cm in total length, in the superficial femoral or popliteal arteries that meets all the angiographic inclusion criteria and none of the exclusion criteria.

Target Lesion Revascularization (TLR)

Re-treatment by an invasive procedure, including atherectomy, angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter of the target lesion. TLRs will be classified as clinically-driven or not clinically-driven through an adjudication process. Diameter stenosis will be determined per angiographic core laboratory assessment.

Target Lesion Revascularization, Clinically-Driven:

A revascularization of the target lesion is considered clinically-driven if the PSVR ≥ 2.5 by duplex ultrasound or if angiography shows a percent diameter stenosis >50% and there is worsening of the Rutherford Becker Clinical Category or ABI that is clearly referable to the target lesion. (Worsening is defined as deterioration (an increase) in the Rutherford Becker Clinical Category by more than 1 (>1) category from the earliest post-procedural measurement or deterioration in the Ankle Brachial Index (ABI) > 0.15 from the maximum early post-procedural level.)

An independent ultrasound and/or angiographic core laboratory will verify that the severity of percent diameter stenosis meets requirements for clinically-driven and will overrule in cases where investigator reports are not in agreement.

Target Limb

The entire limb in which the target lesion is located.

Target Vessel

The entire vessel in which the target lesion is located.

Target Vessel Revascularization (TVR)

Any reintervention in the target vessel.

Target Vessel Revascularization, Clinically Driven

A repeat revascularization procedure (percutaneous or surgical) of a lesion in the target vessel, exclusive of the target lesion site. A revascularization of the target vessel is

considered clinically-drivent the PSVR ≥ 2.5 by duplex ultrasound or if angiography shows a percent diameter stenosis >50% and there is worsening of the Rutherford Becker Clinical Category or ABI that is clearly referable to the target lesion. (Worsening is defined as deterioration (an increase) in the Rutherford Becker Clinical Category by more than 1 (>1) category from the earliest post-procedural measurement or deterioration in the Ankle Brachial Index (ABI) by > 0.15 from the maximum early post-procedural level.)

Thrombosis

The formation or development of thrombus inside a blood vessel, obstructing the flow of blood.

Thrombus

A blood clot within a vessel, which obstructs the flow of blood.

Total Occlusion

100% stenosis within an artery.

Transient Ischemic Attach (TIA)

Brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 24 hours, and without evidence of infarction.

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 protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Vascular Access Complications

Access Site Occlusion:

Access site occlusion is defined as total obstruction of the artery usually by thrombus (but may have other causes) usually at the site of access requiring surgical repair.

Arteriovenous Fistula

A communication between an artery and a vein in which the arterial blood flows directly into a neighboring vein.

Peripheral Embolization

Peripheral embolization is defined as a loss of distal pulse, pain and/or discoloration (especially the toes). This can include cholesterol emboli. The site should indicate whether a peripheral embolization occurred distal to the arterial access site during the procedure or after lab visit but before any subsequent lab visits, requiring therapy.

Pseudoaneurysm

Perforation of the vessel with arterial blood flow outside of the vessel.

Hematoma

Localized mass of extravasated blood ≥ 5 cm that prolongs hospitalization.

Retroperitoneal Bleed

An accumulation of blood in the retroperitoneal space.

Peripheral Ischemia

A restriction in arterial blood flow by stenosis, restenosis or occlusion that, if prolonged, can lead to tissue damage.

Walking Impairment Questionnaire (WIQ)

A disease-specific instrument utilized to characterize walking ability through a questionnaire. It is a measure of patient-perceived walking performance for patients with PAD and/or intermittent claudication.

APPENDIX D: Rutherford-Becker Classification Guidelines

Rutherford-Becker Classification[1] is a classification system of Peripheral Arterial Disease. Determination of Rutherford-Becker Classification is required at the following time points:

- 24 and 36 month follow-up visits
- Unscheduled visits and re-interventions

The Rutherford-Becker Classification is a global assessment based on the clinical description.

Category	Clinical Description
0	Asymptomatic--no hemodynamically significant occlusive disease
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4*	Ischemic rest pain
5*	Minor tissue loss-nonhealing ulcer, focal gangrene with diffuse pedal ischemia
6*	Major tissue loss-extending above transmetatarsal level, functional foot no longer salvageable

*Categories 4, 5, and 6 are also described as critical limb ischemia.

[1] Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997 Sep; 26(3):517-38.

APPENDIX E: Ankle Brachial Index (ABI) Guidelines

Determination of Ankle Brachial Index (ABI) is required for each subject (study treatment limb only) at the following time points:

- 24 and 36 month follow-up visits
- Unscheduled and Re-intervention visits

The ABI assessment is required to be attempted at the required time points given above. If the ABI is not attempted at a required time point, it will be a protocol deviation (except at unscheduled or re-intervention visits). If the ABI result cannot be calculated due to a non-compressible artery, then it will not be a protocol deviation.

Performing the ABI is a fast and effective non-invasive tool for screening for Peripheral Arterial Disease. Interpreting the ABI results are described in the table below.

ABI Results	**Indication**
0.96 or Above	Generally normal
0.81 – 0.95	Mild disease
0.51-0.80	Moderate disease
0.31-0.50	Moderate to severe disease
0.30 or below	Severe disease

Preparing the Patient:

1. The patient should have refrained from smoking for at least 1 hour prior to the testing.
2. It is recommended that the same size cuff is used for both brachial and ankle pressures for an assessment and for each study visit.
3. Have the patient remove shoes, socks/stockings and slacks if they cannot be easily rolled up to the knee. Shirts or blouses should be able to be easily rolled up to allow adequate placement of a blood pressure cuff on the arm. If clothing inhibits placement of the cuff or constricts the extremity, it should be removed.
4. Make sure the patient is comfortable and warm. Cover patient with a sheet or blanket if desired.
5. The patient should be allowed to rest quietly for at least 5 minutes prior to beginning the test.
6. Bilateral ABI is useful at baseline if the target limb has not yet been confirmed. At follow-up visits, only the target limb ABI is required. The database only requires entry of the target limb ABI for all visits.

Automatic vs. Manual Assessment

ABI may be assessed using an automatic ABI machine or assessed manually.

Automatic ABI Assessment

For automatic ABI assessment, please follow the equipment instructions to obtain the ABI readings.

Manual ABI Assessment

For manual ABI assessments please refer to the guidelines below:

Equipment:

- Vascular Doppler with 5 or 8 MHz probe
- Ultrasound gel
- Blood pressure cuff (same size cuff for each subject for all visits is recommended)
- Sphygmomanometer
- Pen, paper, and calculator

Performing the Exam:

1. For first assessment for the subject, select the appropriate size cuff. An inappropriately sized blood pressure cuff will affect your results. It is recommended that the cuff bladder be 20% wider than the extremity diameter.
    a. Use the same size cuff for both arm and ankle measurements.
    b. It is recommended that you use the same size cuff consistently for all visits for the subject.
2. Arm Pressure:
   Obtain brachial systolic pressure per your site's SOC. If using a Doppler probe, follow these guidelines:
    a. Place the appropriate sized cuff midway on the patient's upper arm. Approximately two finger widths should exist between the crease in the antecubital space and the bottom of the cuff. The cuff should not be placed over the elbow area or cover the antecubital space.
    b. Attach the sphygmomanometer.
    c. Squeeze out approximately a dime sized amount of ultrasound gel and spread it over the antecubital space locating the brachial artery using the tip of the Doppler probe. Slowly move the probe across the brachial area until you hear the "whooshing" sound. Once you locate the brachial artery, adjust the volume on the probe so the signal can be easily heard. This position should be maintained throughout the rest of the procedure. To steady your hand (so you don't lose placement) you may gently rest your hand on the patients arm.
    d. Begin inflating the blood pressure cuff. You will continue to hear blood moving through the artery. As you continue to inflate the cuff, the pressure of the cuff will stop the flow of blood through the artery. Stop inflating the cuff approximately 10-20 mmHg past the point where you no longer heard the sound.
    e. Slowly deflate the cuff by 1-2 mm increments. At the point where the sound returns, make note of the location of the gauge needle. Record this as the systolic pressure. Once you have accomplished this you may rapidly deflate the cuff the down to 0 mmHg.
    f. Repeat this procedure on the opposite arm.
    g. If you miss hearing the sound while deflating the cuff-allow 5 minutes before reattempting the procedure. Repeat the steps above.
    h. Record the data collected.
3. Ankle pressure:
    a. Two locations are available for obtaining ankle pressure; the posterior tibial (PT) artery is preferred although you can use the dorsalis pedis (DP) artery. Attempt to locate the PT (located just behind the medial ankle bone) and use this as your measurement. The DP (top of foot) may be used for calculating the ABI only if PT is non-compressible. Be advised that pressing too hard on the DP will obliterate the sound. Gentle pressure is to be used.
    b. Use the same cuff size as was used on the patient's arm. Wrap the cuff snugly around the patient's ankle, just above the foot. Have patient rotate the foot outward
    c. Attach the sphygmomanometer.

d. Squeeze out approximately a dime sized amount of ultrasound gel out over the PT (or DP if needed) and place the probe. Spread the gel around and using the probe listen for the whooshing sound indicating blood flow. When you locate the sound, adjust the volume of the probe and maintain your position for the remainder of the procedure. Again, you may rest your hand gently on the patient's foot to steady it.

e. Begin inflating the blood pressure cuff. You will continue to hear blood moving through the artery. As you continue to inflate the cuff, the pressure of the cuff will stop the flow of blood through the artery. Stop inflating the cuff approximately 10-20 mmHg past the point where you no longer heard the sound.

f. Slowly deflate the cuff by 1-2 mm at a time. When the sound reappears record this as your systolic pressure. Once you have accomplished this you may rapidly deflate the cuff down to 0 mmHg.

g. Repeat this procedure on the other ankle if obtaining bilateral ABIs.

h. If you miss hearing the sound while deflating the cuff-allow 5 minutes before reattempting the procedure. Repeat the steps above.

i. Record the data collected.

Calculating the ABI

1. When both brachial pressures and at least one ankle pressure has been obtained, select the highest brachial value.
2. In patients with diabetes and heavily calcified vessels, the arteries are frequently not compressible. If you miss hearing the whooshing sound after repeated attempts (two or more times at one location) either before inflating the cuff or while deflating the cuff, the vessel is not compressible. Non-compressible arteries may result in artificially elevated pressure which in turn underestimates disease severity. The goal of obtaining an ABI is to measure an artery without significant calcification and results in an ABI value < 1.3.
3. Divide the ankle pressure by the highest brachial pressure. The result is the ABI.

APPENDIX F: Walking Impairment Questionnaire (WIQ) Guidelines

Completion of the Walking Impairment Questionnaire is required for eligible subjects at the following time points:

- 24 and 36 month follow-up visits
- Unscheduled visits and re-interventions

The Walking Impairment Questionnaire is a functional assessment focusing on the difficulty a subject experiences when walking. The questionnaire can be useful in determining the effectiveness of the study treatment by evaluating the subject's severity of symptoms, and walking ability (distance and speed).

The WIQ is an interviewer-administered questionnaire. The interviewer should administer the WIQ by asking the subject the questions as they are presented on the worksheet, and recording all responses in the space provided. In order for the assessment to be evaluable, the subject needs to provide an answer for every question for walking distance and walking speed. A response must be provided for each question. Only in the event an entire group of questions under a numerical category are left blank can this be left blank in the EDC. If a subject does not have experience with stair climbing, do not mark a response and leave the field blank.

The WIQ results from each visit should be recorded on the CRFs for the 24 and 36 month follow-up visits. This form should also be completed if the subject returns for an unscheduled visit or a re-intervention. After each assessment, enter the data into the EDC.

APPENDIX G: 6 Minute Walking Test Instructions

The 6 Minute Walking Test is required at the following time points:

- 24 and 36 month follow-up visits

Instructions

Set Up:

- Measure out 30 meters in geographies using the metric system, or 100 feet for geographies using the English system of measure. Preferably, in a long hallway (without corners or turns) or other flat, hard surface with interval markings every 3 meters, or 10 feet. Use of a treadmill, oval or circular track for this test is not recommended.
- Mark the boundaries of the course with cones or brightly colored tape.
- If possible, use a quiet, straight hallway for the test.
- Have one or more chairs available along the course for the subject to rest in if needed during the test.

Administration:

- Ask the subject to wear comfortable footwear and clothing on the day of the test.
- Do not walk with or behind the subject. If the subject has an oxygen tank do not push the tank, instead have the subject walk with it as he/she would at home.
- Do not conduct the test with multiple people at one time.
- Instruct the subject to walk as far as they can in 6 minutes at their usual pace or at a comfortable pace and to use any walking aids normally used (e.g. a cane).
- Count laps with a lap counter.
- Time the test with a stopwatch.
- Encouragement can affect the outcome of the test. No encouragement should be given to subjects while conducting the test.

APPENDIX H: EQ-5D Instructions

The EQ-5D Questionnaire is required for each subject at the following time points:

- 24 and 36 month follow-up visits
- Unscheduled visits and re-interventions

The EQ-5D is a standardized measure of health status developed by the EuroQuol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

EQ-5D is designed for self-completion by subjects and is intended to reflect the health status at the time of completion. Instructions for completion are included within the questionnaire. It should be completed prior to any other assessments in order to capture the subject's self-assessment prior to discussions with the site personnel.

EQ-5D is two pages in length with two sections, the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, severe problems. The subject is asked to indicate his/her health state by ticking or placing a cross in the box against the most appropriate statement in each of the five dimensions. The decision results in a one digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five digit number describing the respondent's health state.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state.'

Reference: EQ-5D User's Guide, EuroQOL Group, 2009 (www.euroqol.org).

Investigators Responsibilities

1. Have and maintain the resources necessary to conduct the clinical investigation properly.
2. Ensure that conducting the clinical investigation is not nor will not cause a conflict of interest.
3. Obtain from the sponsor information which the clinical investigator judges essential about the device and be familiar with this information.
4. Understanding of the protocol prior to signing it.
5. Compliance with the protocol and any amendments.
6. Support the monitor in their activities to verify compliance with the protocol, to perform source data verification, and to correct case report forms where inconsistencies or missing data is identified.
7. Discuss with the sponsor and monitor any question of modification of the clinical investigation plan and obtain written approval of the sponsor.
8. Ensure the clinical investigation plan is followed by all persons responsible for the conduct of the clinical investigation at the institution. Any deviation must be documented and reported to the sponsor.
9. Make the necessary arrangements to ensure the proper conduct and completion of the clinical investigation.
10. Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject.
11. Ensure that appropriate Institutional Review Board (IRB) or Ethics Committee (EC) approval has been received prior to the start of the clinical investigation at the center.
12. Provide the results from the IRB/EC to the sponsor.
13. Inform the IRB/EC and request opinion and/or approval for any significant change in the clinical investigation plan that has been approved by the sponsor.
14. Inform the IRB/EC about any serious adverse event and/or unanticipated adverse device effect, as applicable.
15. Inform the sponsor about all adverse events, serious adverse events, and unanticipated adverse device effects in a timely manner.
16. Attempt to ensure an adequate recruitment of subjects.
17. Ensure that the subject has adequate information to give informed consent.
18. Ensure that informed consent is obtained and documented.
19. Ensure that clinical records are clearly marked to indicate the subject is enrolled in a particular clinical investigation. If appropriate, subjects enrolled in the clinical investigation must be provided with some means of showing their participation in the investigation, together with identification and compliance information for concurrent treatment measures. Contact addresses/telephone numbers must be provided. If appropriate, the subject's personal physician should, with the subject's agreement, be informed.
20. Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the clinical investigation plan will not require the prior approval of the sponsor or the IRB/EC. Such deviations must not be considered as a breach of agreement but shall be documented and reported to the sponsor.