The DETOUR 2 Clinical Trial

The Detour Endovascular Technique for long OcclUsive fem-pop Revascularization – 2 Clinical Trial

Protocol Number: STP 203 Rev. F

Sponsor:
PQ Bypass, Inc.
1971 Mimont Drive
Milpitas, CA 95035

Issue Date: 16 March, 2020

CONFIDENTIAL

INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: The Detour Endovascular Technique for long OcclUsive fem-pop Revascularization – 2 Trial (The DETOUR 2 Clinical Trial)

PROTOCOL NUMBER & ISSUE: STP 203 Rev. F

STUDY CENTER: _____

(Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree with its content. I agree to perform and conduct the Study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the Study as described in the protocol. I will provide copies of this Protocol and all pertinent information to the Study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the PQ Bypass investigational device and the conduct of the Study according to Good Clinical Practice (GCP), Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2011 (OUS centers only), and any local regulations.

Site PI Name: _____

Site PI Signature: _____ **Date:** _____

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Protocol Synopsis

The Detour Endovascular Technique for long OcclUsive fem-pop Revascularization – 2 Clinical Trial

Protocol Number: STP 203 REV. F
IDE Number: G170083
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Image Transfer Platform: Medidata Rave Imaging, New York, NY, USA

Version Number: Rev. F

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PROTOCOL SYNOPSIS

Sponsor Name:	PQ Bypass, Inc.
Title:	The DETOUR 2 Clinical Trial - The **D**etour **E**ndovascular **T**echnique for long **O**ccl**U**sive fem-pop **R**evascularization – 2 Clinical Trial
Study Description:	Prospective, single-arm, multi-center, international clinical investigation to evaluate the safety and effectiveness of the PQ Bypass System to access, deliver guidewires, and implant stent grafts for a percutaneous femoropopliteal (fem-pop) bypass.
Study Objective:	The safety and effectiveness of the PQ Bypass System will be established by comparing the primary safety and effectiveness endpoints in the IDE Study to safety and effectiveness Performance Goals (PG).
Primary Endpoints:	Primary Efficacy Endpoint The absence of clinically-driven target lesion revascularization and absence of recurrent target lesion diameter stenosis >50% by imaging (e.g., duplex ultrasound peak systolic velocity ratio of >2.5 or invasive angiography) within the stent or immediately 1 cm above or below the treated segment. When both modalities are available, angiography takes precedence. Primary Safety Endpoint Freedom from a major adverse event (MAE) at 30 days post-procedure defined as any occurrence of the following events: Death, Clinically-Driven Target Lesion Revascularization (CD-TLR), Amputation of the Treated Limb, Symptomatic Deep Vein Thrombosis (DVT), Pulmonary Embolism, or procedure-related bleeding requiring any transfusion of packed red blood cells or surgery.
Study Population:	202 subjects and up to 80 roll-in subjects • Rutherford 3 to 5 • Complex TASC C and TASC D lesions • Reference Vessel Diameter 4.5 - 6.7 mm
Clinical Sites:	A maximum of 40 US sites and 10 OUS sites.

Description of Study Intervention:

Investigational Device

PQ Bypass designs and manufactures the PQ Bypass System: comprised of the TORUS Stent Graft System, the PQ Crossing Device and the PQ Snare, which allows a percutaneous bypass procedure in the peripheral vasculature.

Investigational Procedure

Medical history and imaging performed within the previous 180 days may be used for this initial eligibility evaluation. Subjects are required to undergo study related exams, to include venous duplex ultrasound, before the start of the interventional procedure. Patient eligibility will be confirmed via angiography prior to insertion of the study devices.

Investigators will access the target lesion and the corresponding ipsilateral vein using standard percutaneous techniques and devices.

After eligibility confirmation, the PQ Crossing Device and the PQ Snare will be used to deliver a guidewire from the arterial segment proximal to the target lesion, through the femoral vein and back into the reconstituted artery distal to the target lesion.

TORUS Stent Grafts are then deployed in series, starting distally, until the bypass is complete. After placement, the Investigator uses a standard balloon dilation catheter to complete stent apposition, ensuring that the balloon is only inflated within the TORUS Stent Graft lumen.

Participant Duration:

Subjects will return to the study center at 1 month (30 days ±7 days), 6 months (180 days ±30 days), 12 months (360 days ±30 days), 24 months (720 days ±60 days), and 36 months (1080 days ±60 days) following the procedure for a follow-up evaluation. During these visits, subjects will undergo lower-extremity arterial and venous duplex ultrasounds, venous health questionnaires, QOL surveys, walk test (sub-group of study subjects), and be examined for any post-procedural complications or adverse events.

Inclusion Criteria:

General Inclusion Criteria

1. Age > 18 and ≤ 90 years of age.
2. Willing and able to provide informed consent.

3. Subject is willing to undergo all follow-up assessments according to the specified schedule over 36 months.

Clinical Inclusion Criteria

4. Chronic, symptomatic lower limb ischemia defined as Rutherford clinical categories 3, 4, or 5.
5. Venous Clinical Severity Score < 3.
6. Subject is a suitable candidate for angiography and endovascular intervention and, if required, is eligible for standard surgical repair.

Angiographic Inclusion Criteria

7. Symptomatic femoropopliteal chronic total occlusions ≥ 20 cm (TASC D) that can include de novo, restenotic, or in-stent restenotic lesions; *or*

   Symptomatic femoropopliteal lesions ≥ 24 cm (total lesion length) that can include a chronic total occlusion or a ≥70% lesion that includes de novo, restenotic or in-stent restenosis (complex TASC C), by investigator visual assessment.
8. Reference vessel diameter ≥ 4.5 and ≤ 6.7 mm, by investigator visual assessment.
9. Subject has a patent popliteal artery (<50% stenosis) distal to the landing zone
10. Able to successfully access the SFA origin for entry of the crossing device.
11. At least one patent infrapopliteal vessel (<50% stenosis) with run-off to the ankle or foot.
12. A significant stenosis (≥ 50%) or occlusion of an ipsilateral, inflow artery (e.g. aortoiliac, common femoral) must be successfully treated (use of investigational treatment prohibited) prior to treatment of the target lesion. Successful treatment is defined as no complications and less than 30% residual stenosis following intervention.

Exclusion Criteria:

General Exclusion Criteria

1. Participating in another investigational clinical study.
2. Anticipated life expectancy less than 1 year or medical comorbid condition(s) that could limit the subject's ability to comply with the requirements of the trial.

3. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.

Clinical Exclusion Criteria

4. History of deep vein thrombosis on either limb.
5. Thrombophlebitis, within the previous 30 days.
6. Planned amputation of the target limb, including minor amputations.
7. Prior distal amputation (above the transmetatarsal) of the target limb.
8. Known or suspected active infection at the time of the procedure (e.g., WIfI foot infection grade 3: Severe infection. Local infection with systemic inflammatory response syndrome [SIRS]).
9. Rutherford clinical category 0, 1, 2 or 6.
10. Has acute or chronic renal disease with GFR ≤ 30 ml/min per 1.73 m^2 and/or elevated serum creatinine >2.5mg/dL (220μmol/L) or on dialysis.
11. Known hypersensitivity/allergy to the investigational devices and/or required pharmacotherapy that cannot be safely managed.
12. Morbid obesity that does not allow for safe vascular access or imaging.
13. Subject has a known coagulopathy or has bleeding diatheses, thrombocytopenia with platelet count less than 100,000/microliter or INR > 1.8.
14. Requires coronary or peripheral procedure within 30 days prior to or planned within 30 days post treatment of the target lesion.
15. Has a known history of intracranial bleeding or aneurysm, myocardial infarction or stroke within the last 3 months.
16. Subject is pregnant or breast-feeding.

Angiographic Exclusion Criteria

17. Stent within 3 cm of SFA ostium.
18. Previous bypass surgery on the target limb.
19. Subject has significant disease or obstruction (≥50%) of the inflow tract that has not been successfully treated at the

time of the index procedure (success measured as ≤30% residual stenosis, without complication)

20. Presence of aneurysm or acute thrombus in the target limb.
21. Thrombolysis of the target vessel within 72 hours prior to the index procedure, where complete resolution of the thrombus was not achieved.

Table 1: Schedule of Assessments

Activity	Initial Eligibility	Pre Procedural Baseline Screening	Procedure	Discharge	Follow-Up Visits				
					1M ± 7D (30D ±7D)	6M ± 30D (180D ±30D)	12M ± 30D (360D ±30D)	24M ± 60D (720D ±60D)	36M ± 60D (1080D ±60D)
Informed Consent/HIPAA *(within 30 days of enrollment)*	X								
Review of Inclusion/Exclusion Criteria	X	X	X						
Pre-Procedural Imaging[1] (CTA, MRA, Angio, etc.)	X								
Pre-Procedural Venous Ultrasound	X								
Medical History/Demographics		X							
Brief Physical Exam/Health Status		X		X	X	X	X	X	X
Routine Laboratory Tests (CBC and Chem-7)		X							
Serum Creatinine to Calculate eGFR		X							
Ankle-Brachial Index (or Toe-Brachial Index[2])		X			X	X	X	X	X
Rutherford Assessment		X			X	X	X	X	X
Venous Clinical Severity Score and Villalta Scale		X			X	X	X	X	X
Final Eligibility Angiogram/Venogram or venous ultrasound[3]			X						
Device Accountability			X						
Venous Ultrasound[4] and Venous Observation Scale					X	X	X	X	X
Arterial Ultrasound[4]					X	X	X	X	X
Stent Graft X-Ray							X		
Adverse Event Assessment			X	X	X	X	X	X	X
Dual Antiplatelet Therapy[5]		X	X	X	X	X	X	X	X
VascuQOL		X			X		X		
EQ-5D-5L QOL		X			X		X		
SF-12		X			X		X		
6 Minute Walk Test[6]		X			X		X		

[1] Pre-procedure imaging performed within 180 days of baseline procedure.

[2] Perform Toe Brachial Index (TBI) only if unable to reliably assess ABI reading. Tests are performed in resting state.

[3] Angiography performed throughout the index procedure. Angiography required to be submitted to the angiographic core lab for all target limb revascularization procedures.

[4] Duplex Ultrasound is to be completed at each follow-up visit.

[5] Effective anticoagulation therapy should be maintained throughout the procedure (minimum ACT >250 seconds is recommended). Dual anti-platelet or anti-coagulation therapy is recommended for at least three years. Refer to Section 4.2.10 for full recommendations

[6] The 6-Minute Walk Test is not routinely performed at all clinical sites; therefore, select sites shall complete a 6MWT on select subjects as agreed upon. This will therefore result in a sub-group of clinical sites and subjects and not be studywide.

1.0 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Systematic reviews indicate that PAD affects more than 200 million people worldwide—and the prevalence of PAD is increasing as "baby boomers" enter high-risk age groups. The field of endovascular medicine has evolved to treat this growing population; however, an effective minimally-invasive treatment for long and complex lesions of the superficial femoral artery (SFA) remains a significant unmet need.

Treatment options for patients with long and complex femoropopliteal lesions (≥ 24 cm in length, hemodynamically-significant) are not optimal, and choosing a treatment strategy for this category of lesion presents a clinical dilemma for both the physician and the patient. Endovascular devices, while less invasive than open femoropopliteal bypass surgery, were initially developed for shorter lesions, and have demonstrated reasonable effectiveness in lesions < 20 cm, with 12-month patency rates ranging from 76% to 86%. When applied to lesions ≥ 24 cm, however, these same endovascular devices have not demonstrated comparable medium-term effectiveness, with 12-month patency rates ranging from 42% to 64%. Complicating factors include:

- Amplified biologic reaction to treatment
- Suboptimal luminal gain with high residual resistance to flow
- Profunda collateral competition
- Poor runoff
- Distal embolization

1.2 DEVICE DESCRIPTION

PQ Bypass designs and manufactures the PQ Bypass System which allows a percutaneous bypass procedure in the peripheral vasculature. The PQ Bypass System is comprised of the TORUS Stent Graft System, the PQ Crossing Device and the PQ Snare.

1.2.1. The PQ Crossing Device

The PQ Crossing Device (**Figure 1**) is a spring-loaded delivery tool that utilizes a 0.025" Nitinol Needle with a 15 mm throw that exits approximately 45° to the PQ Crossing Device Shaft. The PQ

Crossing Device is an 8Fr compatible device with 135 cm working length with dual 0.014" guidewire (GW) ports; an Rx GW Port and a Needle GW Port. The PQ Crossing Device also incorporates an intra-luminal Stabilizer and a Platinum-Iridium Marker Band used to support and direct needle deployment, respectively. The PQ Crossing Device features are controlled using the Outer Handle and the Button on the PQ Crossing Device Handle.

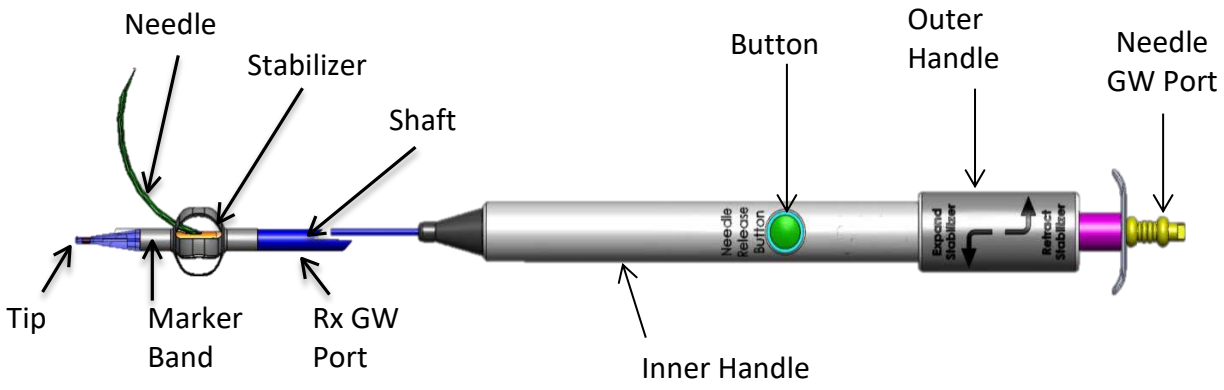

Figure 1: The PQ Crossing Device

1.2.2. <u>The PQ Snare</u>

The PQ Snare (**Figure 2**) is an over-the-wire endovascular snare that utilizes dual, radiopaque NiTi cages to provide scaffold support to the femoral vein and to snare guidewires. The PQ Snare is 95 cm in length and is compatible with 7Fr sheaths and 0.014" guidewires. The dual NiTi cages deploy to a maximum of 11 mm at the apex and can be secured at a fixed diameter at any point during expansion (**Figure 3**).

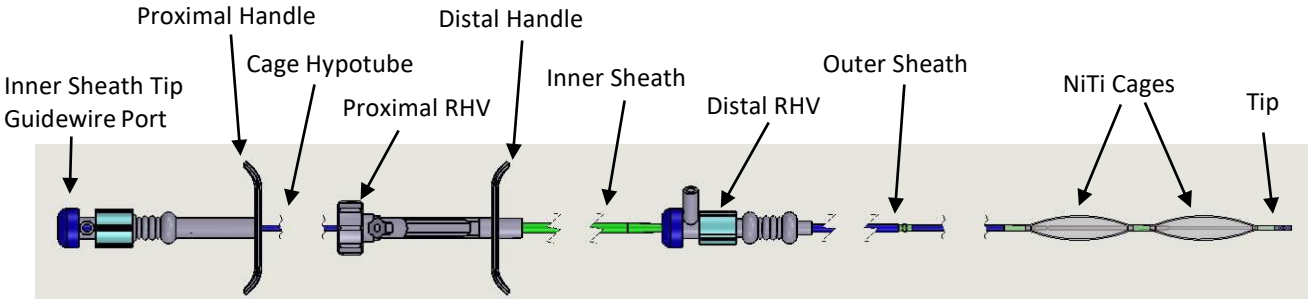

Figure 2: The PQ Snare

Figure 3: The PQ Snare Cases Deployed

1.2.3. TORUS Stent Graft

The TORUS Stent Graft (**Figure 4**) is a flexible, self-expanding composite structure made of a NiTi-wire frame encapsulated in an expanded Polytetrafluorethylene (ePTFE) film.

Figure 4: The TORUS Stent Graft

1.2.4. TORUS Stent Graft Delivery System

The TORUS Stent Graft Delivery System (**Figure 5**) is an 8Fr system. It is 0.035" guidewire compatible and has a 135 cm working length. The TORUS Stent Graft System is a familiar design which uses an outer sheath to maintain the TORUS Stent Graft in a compressed state. The delivery system has radiopaque markers on both the proximal and distal ends of the TORUS Stent Graft landing zone (area where stent graft is located), as well as a marker band on the outer sheath to allow visualization of the sheath during deployment.

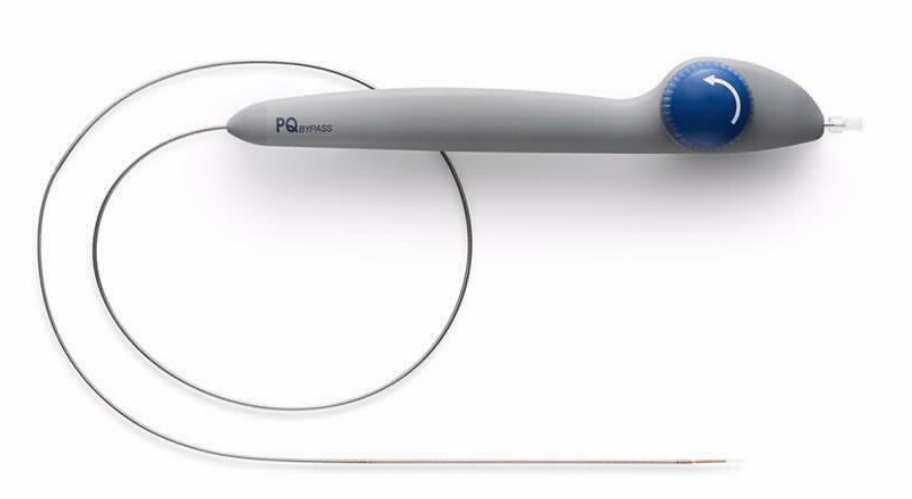

Figure 5: TORUS Stent Graft Delivery System

1.3 REGULATORY STATUS

The PQ Bypass System received CE Mark in March 2017.

1.4 PROPOSED INTENDED USE

The PQ Bypass System is intended to improve blood flow in patients with peripheral arterial disease in symptomatic femoropopliteal lesions due to chronic total occlusions ≥ 20 cm (TASC D) that can include de novo, restenotic, or in-stent restenotic lesions; or total lesion lengths ≥24 cm that can include chronic total occlusions or a ≥70% lesion that includes de novo, restenotic or in-stent restenosis (complex TASC C).

The PQ Crossing Device is intended to facilitate placement and positioning of guidewires in the distal peripheral vasculature.

The PQ Snare is intended for retrieval and manipulation of atraumatic foreign bodies in the distal peripheral vasculature.

1.5 CE MARK STUDY – DETOUR I

To evaluate the preliminary safety and effectiveness of the PQ Bypass System, the sponsor conducted the DETOUR I Clinical Trial (DETOUR I). This is a prospective, multi-center, single-arm, independently adjudicated study to assess the safety and effectiveness of the PQ Bypass System in patients with long-segment SFA disease. A total of 78 subjects were enrolled, and 77 subjects (81 limbs) were treated. Follow-up to one year has been completed, and follow-up to three years is ongoing. A brief update on the preliminary one-year results of DETOUR I is included below for context for the discussion of proposed modifications to the design of

the pivotal US IDE study. An interim study report will be included in the IDE supplement for this protocol modification.

DETOUR I enrolled patients presenting with severe claudication, rest pain, or ischemic ulceration (Rutherford category 3-5). The primary efficacy endpoint was primary patency at six months, defined as freedom from clinically significant stenosis (≥ 50%) by duplex ultrasound (PSVR > 2.5) within the stent graft or immediately above or below the treated segment and without clinically-driven reintervention within the stented segment. The primary safety endpoint was major adverse clinical events at one month, defined as the composite of death, target vessel revascularization, and major amputation of the target limb. **Table 2** below shows the lesion inclusion criteria and the actual lesion charactieristics enrolled in DETOUR I, and **Table 3** below summarizes the demographics of the patients enrolled in the study.

Table 2: Baseline Lesion Characteristics in DETOUR I

	Inclusion Criteria	Actual Lesions Enrolled* (n = 77/81)
SFA lesion length, mm (Mean ± SD) Range (N)	≥100 mm	371 mm ± 55 222 mm – 472 (81/81)
Chronic total occlusion, (%, n/N)	ANY	96% (78/81)
In Stent Restenosis (ISR), (%, n/N)	ANY	2.4% (2/81)
Calcification, (%, n/N) Mild Moderate Severe	ANY	 18.8% (15/80) 13.8% (11/80) 67.5% (54/80)
Vessel Run-Off	≥ 1 PATENT TIBIAL VESSEL	
1		7.7% (6/78)
2		29.5% (23/78)
3		62.8% (49/78)

*Analysis based on 81 treated lesions; where sample size is less than 81, complete lesion data were not available.

Table 3: Patient Demographics and Clinical Characteristics in DETOUR I

Clinical Characteristics	N=77 Subjects
Male (%, n/N)	83.1% (64/77)
Age (Years) (mean ± SD)	64.1 ± 7.2
Diabetes Mellitus (%, n/N)	24.7% (19/77)
Hypertension (%, n/N)	83.1% (64/77)
Hypercholesterolemia (%, n/N)	39.0% (30/77)
History of CAD or MI (%, n/N)	42.9% (33/77)
History of Smoking (%, n/N)	87.0% (67/77)
Previous Peripheral Intervention (%, n/N)	29.9% (23/77)
ABI (mean ± SD)	0.64 ± 0.17 (81 Limbs)
Rutherford Category 3	93.0% (75/81 Limbs)
Rutherford Category 4-5	7.0% (6/81 Limbs)

CLINICAL ENDPOINTS

The primary safety endpoint was major adverse events (MAEs) at 30 days, defined as the composite of death, target vessel revascularization, and target limb amputation. At 30 days, the MAE rate was 6.5% (5/77), consisting of five target vessel revascularizations (TVR). At one year, the MAE rate was 26%, consisting of 19 TVR and one death (due to ischemic stroke at 114 days post-procedure). Two subjects had deep vein thrombosis (DVT). One DVT was secondary to trauma in a patient who received a diagnosis of vasculitis following enrollment. The second DVT was secondary to right inguinal hernia repair, and the subject also stopped following the DAPT regimine. Both were treated with medical therapy and resolved without sequelae. **Table 4** summarizes the safety outcomes for the DETOUR I Clinical Trial.

Table 4: DETOUR I Safety Outcomes

Safety Outcomes	30 Days		12 Months	
	Subjects	Limbs	Subjects	Limbs
Death	0% (77/77)	n/a	1.2% (1/77)	n/a
TVR	6.5% (5/77)	6.2% (5/81)	25.0% (19/76)	23.8% (19/80)
Major Amputation of Ipsilateral Limb	0% (0/77)	0% (0/81)	0% (0/76)	0% (0/80)
MAE (Death, TVR, Amputation)	6.5% (5/77)	6.2% (5/81)	26.0% (20/77)	24.7% (20/81)
Deep Vein Thrombosis	1.3% (1/77)	1.2% (1/81)	2.6% (2/76)	2.5% (2/80)
Pulmonary Embolism	0.0% (0/77)	0.0% (0/81)	0.0% (0/76)	0.0% (0/81)
Bleeding event requiring transfusion > 2 units of packed red blood cells.	0% (0/77)	0% (0/81)	0% (0/76)	0% (0/80)
Bleeding event requiring any transfusion	1.3% (1/77)	1.2% (1/81)	1.2% (1/76)	1.3% (1/80)

Primary patency was 93.8% (76/81) and 73.8% (59/80) at 30 days and one year, respectively. At one year, an additional five subjects remained patent after reintervention for non-occlusive disease, and nine more had successfully revascularized graft occlusions, for assisted and secondary patency rates of 80.0% and 93.8%, respectively.

In summary, this initial experience demonstrates that the endovascular bypass with the PQ Bypass System could be accomplished with 98.8% technical success (defined as the successful delivery of the investigational device to the identified area and removal of the delivery system) in extremely long ($\geq$ 200 mm), calcified, primarily CTO lesions, with a 93.5%

freedom from MAE to 30 days (five early revascularizations). Primary patency was excellent at 30 days, and 74% of subjects remained patent at one year. This primary patency rate was achieved in patients with a mean lesion length of 371 mm.

1.6 RISKS AND BENEFITS

1.6.1. Risks

There are standard risks associated with any interventional procedure or stent graft placement as well as risks specific to the PQ Bypass System and procedure. Risks associated with any interventional procedure include access site hemorrhage or hematoma, access site pain, acute vessel closure, infection, renal insufficiency/failure due to excessive contrast load, and death. The risks stated below concern each component manufactured by PQ Bypass and their use in the PQ Bypass System procedure.

Possible risks related to the PQ Crossing Device and the PQ Snare include, but are not limited to, the following: access vessel (arterial/venous) occlusion, amputation, bleeding complications; death, device malfunction/failure, embolism (peripheral or pulmonary), fever in absence of infection, hemorrhage or hematoma, infection local or systemic including bacteremia or septicemia, myocardial infarction, pain (insertion site, leg and/or foot), shock, stroke or transient ischemic attack, thrombosis, vessel wall trauma (dissection, perforation or rupture), vessel spasm, and/or venous flow disruption (deep vein thrombosis, phlebitis, leg swelling and/or development of varicose veins).

Possible risks related to the TORUS Stent Graft System include, but are not limited to, the following: access vessel (arterial/venous) occlusion, amputation, aneurysm or pseudoaneurysm, arteriovenous fistula, bleeding complications, death, device or deployment malfunction/failure, embolism (peripheral or pulmonary), fever in absence of infection, hemorrhage or hematoma, infection local or systemic including bacteremia or septicemia, malapposition or migration, malposition, myocardial infarction, pain (insertion site, leg and/or foot), side branch occlusion stroke or transient ischemic attack, thrombosis, vessel wall trauma (dissection, perforation or rupture), vessel spasm, venous flow disruption (deep vein thrombosis, phlebitis, leg swelling and/or development of varicose veins), and/or worsening claudication.

Additionally, subjects will be exposed to risks associated with conscious sedation, use of contrast and procedural medications. Subjects will be asked to take anti-platelet medication for this study, such as aspirin for life and Plavix (clopidogrel) or Ticlid (ticlopidine) for length of follow-up. These medications have been approved to reduce the risk of cardiovascular events. An Investigator will discuss with each subject the standard risks associated with these medications.

Risk will be mitigated by working with Investigators who are experienced and skilled in endovascular techniques including use of re-entry tools and stent graft placement. Additionally, each Investigator will be thoroughly trained on proper device operation prior to device use. Risks will also be minimized in this study by adhering to the inclusion/exclusion criteria. For example, subjects with known allergies or contraindications to study medications that cannot be medically managed otherwise (e.g. contrast, anti-platelet, heparin) will be excluded. Risks associated with device malfunctions or failures will be minimized through bench and in-vivo animal verification and validation testing prior to use in this study.

1.6.2. Benefits

Patients included in this study have lesions that are challenging to treat with conventional endovascular means. Based on previous treatments using commercially available devices and PQ Bypass's bench and animal testing, it is expected that the participants in this study will have their lesions successfully treated without the need for surgery. Bypassing lesions with the PQ Bypass System may allow physicians to treat challenging lesions in the femoral-popliteal artery percutaneously, thereby avoiding the risks and morbidity of more invasive procedures such as surgical bypass or amputation.

2.0 TRIAL OBJECTIVES

The objectives of the IDE Study are to evaluate the safety and effectiveness of the PQ Bypass System to access, deliver guidewires and implant stent grafts for a percutaneous fem-pop bypass. The safety and effectiveness of the PQ Bypass System will be established by comparing the primary safety and effectiveness endpoints in the IDE Study to safety and effectiveness Performance Goals (PG).

- The primary safety endpoint will compare Major Adverse Event (MAE) at 30 days for the PQ Bypass System Group to a safety Performance Goal (PG)

derived from literature, including an aggregate of published trial data and the Summary of Safety and Effectiveness Data (SSED) of the PMAs of approved devices.

- The primary effectiveness endpoint will compare primary patency at 12 months of the PQ Bypass System Group to an effectiveness PG derived from literature, including an aggregate of published trial data and the Summary of Safety and Effectiveness Data (SSED) of the PMAs of approved devices.

3.0 SELECTION AND WITHDRAWAL OF SUBJECTS

3.1 INCLUSION CRITERIA

All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this trial:

General Inclusion Criteria

1. Age > 18 and ≤ 90 years of age.
2. Willing and able to provide informed consent.
3. Subject is willing to undergo all follow-up assessments according to the specified schedule over 36 months.

Clinical Inclusion Criteria

4. Chronic, symptomatic lower limb ischemia defined as Rutherford clinical categories 3, 4, or 5.
5. Venous Clinical Severity Score < 3.
6. Subject is a suitable candidate for angiography and endovascular intervention and, if required, is eligible for standard surgical repair.

Angiographic Inclusion Criteria

7. Symptomatic femoropopliteal chronic total occlusions ≥ 20 cm (TASC D) that can include de novo, restenotic, or in-stent restenotic lesions; *or*

   Symptomatic femoropopliteal lesions ≥ 24 cm (total lesion length) that can include a chronic total occlusion or a ≥70% lesion that includes de novo, restenotic or in-stent restenosis (complex TASC C), by investigator visual assessment.
8. Reference vessel diameter ≥ 4.5 and ≤ 6.7 mm, by investigator visual assessment.
9. Subject has a patent popliteal artery (<50% stenosis) distal to the landing zone

10. Able to successfully access the SFA origin for entry of the crossing device.
11. At least one patent infrapopliteal vessel (<50% stenosis) with run-off to the ankle or foot.
12. A significant stenosis (≥ 50%) or occlusion of an ipsilateral, inflow artery (e.g. aortoiliac, common femoral) must be successfully treated (use of investigational treatment prohibited) prior to treatment of the target lesion. Successful treatment is defined as no complications and less than 30% residual stenosis following intervention.

3.2 EXCLUSION CRITERIA

Subjects will be excluded from participating in this trial if they meet any of the following exclusion criteria:

General Exclusion Criteria

1. Participating in another investigational clinical study.
2. Anticipated life expectancy less than 1 year or medical comorbid condition(s) that could limit the subject's ability to comply with the requirements of the trial.
3. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.

Clinical Exclusion Criteria

4. History of deep vein thrombosis on either limb.
5. Thrombophlebitis, within the previous 30 days.
6. Planned amputation of the target limb, including minor amputation.
7. Prior distal amputation (above the transmetatarsal) of the target limb.
8. Known or suspected active infection at the time of the procedure (e.g., WIfI foot infection grade 3: Severe infection. Local infection with systemic inflammatory response syndrome [SIRS]).
9. Rutherford clinical category 0, 1, 2 or 6.
10. Has acute or chronic renal disease with GFR ≤ 30 ml/min per 1.73 m^2 and/or elevated serum creatinine >2.5mg/dL (220µmol/L) or on dialysis.

11. Known hypersensitivity/allergy to the investigational devices and/or required pharmacotherapy that cannot be safely managed.
12. Morbid obesity that does not allow for safe vascular access or imaging.
13. Subject has a known coagulopathy or has bleeding diatheses, thrombocytopenia with platelet count less than 100,000/microliter or INR > 1.8.
14. Requires coronary or peripheral procedure within 30 days prior to or planned within 30 days post treatment of the target lesion.
15. Has a known history of intracranial bleeding or aneurysm, myocardial infarction or stroke within the last 3 months.
16. Subject is pregnant or breast-feeding.

Angiographic Exclusion Criteria

17. Stent within 3 cm of SFA ostium.
18. Previous bypass surgery on the target limb.
19. Subject has significant disease or obstruction (≥50%) of the inflow tract that has not been successfully treated at the time of the index procedure (success measured as ≤30% residual stenosis, without complication)
20. Presence of aneurysm or acute thrombus in the target limb.
21. Thrombolysis of the target vessel within 72 hours prior to the index procedure, where complete resolution of the thrombus was not achieved.

3.3 WITHDRAWAL OF SUBJECTS

Each subject may voluntarily withdraw his/her participation from the study at any time without jeopardy or prejudice. If a subject prematurely terminates from the study, the reason for study termination will be recorded and the results will be tabulated by number and percent for each category. If termination is a result of an adverse event or death, an Adverse Event Form will also be completed. Subjects who withdraw consent after treatment will have their data evaluated until the time of their withdrawal.

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study, or the adverse event is otherwise explained.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to loss to follow-up, withdrawal, or non-adherence with required assessments. Three attempts shall be made to contact subjects who do not return for study follow-up visits. The final attempt shall include a certified letter to the subject regarding study participation. If these subjects cannot be locatedat the final scheduled visit, they will be considered lost to follow-up. If they are contacted but refuse to return for visits, they will be considered withdrawals. Subjects shall be encouraged to complete a final study exit visit at the time of withdrawal to assess for safety. Data collected up to the time of loss to follow-up or withdrawal will be maintained in the study database and used for analysis purposes, as appropriate. These subjects will not be replaced.

4.0 TRIAL DESIGN

4.1 DESCRIPTION OF TRIAL DESIGN

Prospective, single-arm, multi-center, international clinical investigation to evaluate the safety and effectiveness of the PQ Bypass System to access, deliver guidewires, and implant stent grafts for a percutaneous femoropopliteal (fem-pop) bypass.

4.2 TRIAL ENDPOINTS

4.2.1 Primary Effectiveness Endpoint

The absence of clinically-driven target lesion revascularization and absence of recurrent target lesion diameter stenosis >50% by imaging (e.g., duplex ultrasound (peak systolic velocity ratio of

>2.5) or invasive angiography) with the stent or immediately 1 cm above or below the treated segment. When both modalities are available, angiography takes precedence..

4.2.2 Primary Safety Endpoint

Freedom from a major adverse event (MAE) at 30 days post-procedure defined as any occurrence of the following events: Death, Clinically-Driven Target Lesion Revascularization (CD-TLR), Amputation of the Treated Limb, Symptomatic Deep Vein Thrombosis (DVT), Pulmonary Embolism, or procedure-related bleeding requiring any transfusion of packed red blood cells or surgery.

4.2.3 Secondary Endpoints

1. Major Adverse Events (MAE) at 6, 12, 24 and 36 months
2. Major Adverse Limb Event (MALE) defined as above-ankle amputation or major reintervention including placement of a new bypass graft, interposition graft, thrombectomy, or thrombolysis
3. Major bleeding is defined as any bleeding event requiring transfusion of ≥2 units packed red blood cells (PRBC) or surgical repair through 30 days
4. Symptomatic Deep Vein Thrombosis (DVT) on ipsilateral limb at 30 days and 6, 12, 24 and 36 months
5. Pulmonary embolism at 30 days and 6, 12, 24 and 36 months
6. Perioperative myocardial infarctions through 30 days
7. Hematoma ≥ 8 cm related to the device or procedure through 30 days
8. The combined rate of death, target lesion revascularization (TLR), index limb amputation, and an increase in Rutherford Clinical~~Becker~~ Classification by 2 classes (comparing pre- to post-procedural assessments) at 30 days and 6, 12, 24 and 36 months
9. Stent graft separation and migration identified via ultrasound imaging at 30 days and 6, 12, 24 and 36 months
10. Stent graft separation and migration identified via X-ray at 12 months
11. Stent graft fracture identified via X-ray at 12 months

12. Technical Success defined as successful delivery of the investigational devices to the identified area and removal of delivery system
13. Procedural Success defined as successful delivery of the investigational devices to the identified area and removal of delivery system in the absence of in-hospital MAEs
14. Clinical Success defined as limb ischemia improvement as assessed by Rutherford Clinical Classification (improvement in scale by ≥1) at 30 days and 6, 12, 24 and 36 months
15. Limb ischemia by Rutherford Clinical - Classification through follow-up at 30 days and 6, 12, 24 and 36 months
16. Primary Patency at 30 days and 6, 24 and 36 months
17. Primary assisted patency defined as revascularization of non-occlusive (<99%) stenosis within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis at 30 days and 6, 12, 24 and 36 months
18. Secondary patency defined as: revascularization of occlusion (100%) within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis at 30 days and 6, 12, 24 and 36 months
19. Target Vessel Revascularization defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel at 30 days, 6, 12, 24 and 36 months
20. Ankle-Brachial Index (ABI) or Toe Brachial Index (TBI) of both the index limb and contralateral limb at 30 days and 6, 12, 24 and 36 months
21. Number of major index limb amputations at 30 days and 6, 12, 24 and 36 months
22. Major procedure-related infections within 30 days
23. Length of post-procedure hospital stay
24. Length of ICU stay
25. Hospital re-admissions through 30 days
26. Change from baseline in VascuQol QOL Score at 30 days and 12 months

27. Change from baseline in EQ-5D-5L QOL Score at 30 days and 12 months
28. Change from baseline in Duplex Venous Observation Scale at 30 days and 6, 12, 24 and 36 months
29. Change from baseline in Villalta and Venous Clinical Severity (VCSS) Scales at 30 days and 6, 12, 24 and 36 months
30. SF-12 Score at Baseline, 30 days and 12 months

4.2.4 Health Economics Analysis

Health care costs and incremental cost-effectiveness for the study population will be assessed throughout through 12 months. The following data elements will be collected for each study subject.

1. Quality-of-life outcome measures will be collected at Baseline, 30 days and 12 months from date of enrollment utilizing the EQ-5D-5L questionnaire
2. Procedure and follow-up cost data, including rehospitalizations, will be collected through 12 months from the date of enrollment.
3. Length of post-procedure hospital stay
4. Length of ICU stay

Follow-up resource utilization and cost data will be collected through 12 months from the date of enrollment. Data to be collected may include, but are not limited to copies of the subjects' hospital bills (UB04) and/or itemized hospital bills. The following personal health information from the UB04 may be collected but not limited to:

1. Subject's hospital admission date
2. Number of devices used
3. Subject's hospital discharge date
4. Subject's procedure date
5. ICD-10 diagnosis and procedure codes, HCPCS and CPT codes
6. Itemized and total charges for hospitalizations
7. Number and duration of admissions to rehabilitation hospitals, nursing homes and other chronic care facilities (and whether the admission was related to PAD and its treatment)

8. Self-reported measures of outpatient medical resource utilization over the course of the follow-up period

4.2.5 Subgroup Analysis

A multivariate logistic regression model will be fit with independent variables (unique for safety and effectiveness analyses) for the subgroup levels as well as the baseline characteristics. Separate baseline characteristics will be developed for safety and effectiveness analyses.

With respect to the primary safety endpoint, the following baseline characteristics will be compared across the subgroups:

- Age (years)
- Gender
- History of smoking
- History of diabetes
- Previous peripheral interventions
- Renal insufficiency
- Congestive heart failure
- Lesion length (cm)
- TASC II classification
- Rutherford classification
- Number of run-off vessels

With respect to the primary effectiveness endpoint, the following baseline characteristics will be compared across the subgroups:

- Gender
- History of smoking
- History of diabetes
- Previous peripheral interventions
- Lesion length (cm)
- TASC II classification
- Rutherford clinical classification
- Number of run-off vessels

Any differences that persist after this adjustment will require further investigation to understand the underlying cause for the observed differences.

4.2.6 Additional Analyses

1. 6 Minute Walk Test at Baseline, 30 days and 12 months
2. Comparison the Open Bypass Primary Patency (Flow vs. No-Flow) at 12 months

4.3 SAMPLE SIZE

Up to 202 subjects, excluding elective roll-ins, with atherosclerotic lesions of the native superficial femoral artery (SFA) or the superficial femoral and proximal popliteal arteries, suitable for treatment with PQ Bypass System will be enrolled.

At least 50% of subjects will be enrolled in the U.S. and no single site will enroll greater than 20% of all subjects.

The first two Subjects enrolled and treated at each site may be considered roll-in subjects. Roll-in subjects will be pre-specified.

4.4 INVESTIGATIONAL SITES

The clinical trial will be conducted at up to 40 clinical sites in the United States and up to 10 sites in Europe.

A single investigational site shall not enroll more that 20% of the total planned trial population (i.e., 42 subjects) without the prior written approval of the Sponsor.

4.5 DURATION OF SUBJECT PARTICIPATION

Subjects enrolled in the trial will participate for approximately 36 months (3 years).

4.6 EARLY STUDY TERMINATION

PQ Bypass reserves the right to terminate the study at any time, but intends only to exercise this right for valid scientific or administrative reasons related to protection of subjects. Investigators and associated EC and CA will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study

- A decision on the part of PQ Bypass to suspend or discontinue development of the device

4.7 WRITTEN INFORMED CONSENT

Subjects who meet general and clincal entry criteria will be asked to sign the study specific Ethics Committee (EC) or Institutional Review Board (IRB) approved Informed Consent Form(s) (**Appendix I**) before any study-specific tests or procedures are performed. Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent Form, the subject may not be eligible to participate if he/she fails screening criteria.

4.8 ENROLLMENT

According to ISO 14155:2011, enrollment in the study occurs at the time of informed consent; however, for the purposes of this study, only subjects who are consented and meet all the study inclusion criteria and none of the study exclusion criteria, venous and arterial access has been achived and study device advanced beyond the sheath will be considered enrolled into the study. Therefore, the enrollment date (Day 0) will be the date of the study index procedure; the enrollment date will not be the date of informed consent for this study. Subjects in whom the PQ Bypass System is inserted into the vascular and/or the procedure was aborted without treatment with the device shall be followed through discharge for safety only and allowed to exit the study.

Investigators will access the target artery and the corresponding ipsilateral vein using standard percutaneous techniques and devices. Patient eligibility will be confirmed prior to insertion of the study device, based on procedural angiogram and sheath placement.

4.9 STUDY PROCEDURES

Subjects will return to the study center at 1 month (30 days ±7 days), 6 months (180 days ±30 days), 12 months (360 days ±30 days), 24 months (720 days ±60 days), and 36 months (1080 days ±60 days) following the procedure for a follow-up evaluation. The subject will undergo lower-extremity arterial and venous duplex ultrasounds, venous health questionnaires, QOL surveys, walk test, and examined for any post-procedural complications or adverse events.

4.9.1 Initial Eligibility

After subjects have signed an informed consent form and before the scheduled interventional procedure, subjects will undergo an

initial eligibility evaluation by the investigator. Medical history within the previous 30 days and imaging performed within the previous 180 days may be used for this initial eligibility evaluation. The evaluation may consist of the following:

- Pre-procedural imaging (CT, MRA, Angio, etc.)
- Pre-procedural venous ultrasound
- Review of inclusion/exclusion criteria

Subject eligibility and pre-procedure imaging studies will be reviewed to assess subject eligibility. This process may be done in collaboration with a screening committee, clinical site investigators, core lab assessment, medical advisory committee, etc. in an effort to assist the sites in eligibility requirements.

4.9.2 Baseline Evaluation

Subjects will undergo a baseline evaluation. This evaluation may be conducted from an office visit within the previous 30 days. The evaluation will consist of the following:

- Subject's demographic data (sex and date of birth)
- Medical and surgical history review, including peripheral vascular history
- Rutherford clinical category
- Venous Clinical Severity Score
- Villalta Scale
- Routine Laboratory Tests (CBC and Chem-7; urine pregnancy test, if applicable)
- eGFR
- Ankle Brachial Index or Toe-Brachial Index
- EQ-5D-5L QOL survey
- VascuQOL survey
- SF-12
- 6-Minute Walk Test (subgroup of subjects only)
- Review of inclusion/exclusion criteria

Note: The 6-Minute Walk Test is not routinely performed at all clinical sites; therefore, select sites shall complete a 6MWT on select subjects as agreed upon. This will therefore result in a sub-group of clinical sites and subjects and not be studywide.

4.9.3 Vascular Access and Guidewire Delivery

Investigators will access the target lesion and the corresponding ipsilateral vein using standard percutaneous techniques and devices. Patient eligibility will be confirmed prior to insertion of the study device, based on procedural imaging and sheath placement.

After eligibility confirmation, the PQ Crossing Device and the PQ Snare will be used to deliver a guidewire from the arterial segment proximal to the target lesion, through the femoral vein and back into the reconstituted artery distal to the target lesion. The number of deployment attempts for guidewire placement access at each anastomosis will be recorded.

4.9.4 TORUS Stent Graft Placement

TORUS Stent Grafts of appropriate dimension are selected by investigators visual estimates of arterial diameter. SGs are then deployed in series, starting distally, until the bypass is complete. After placement, the Investigator uses a standard balloon dilatation catheter to complete stent apposition, ensuring that the balloon is only inflated within the TORUS Stent Graft's lumen.

4.9.5 Anticoagulation and Dual Antiplatelet Therapy

Effective anticoagulation therapy should be maintained throughout the procedure with heparin (per hospital or institutional standards, recommending a minimum of ACT >250) or a clinically acceptable alternative of the treating physician's choice. Subjects must be treated with antiplatelet and/or anticoagulation for a minimum of three years. **Table 5** shows the recommendation for administration of these medications, but the final decision is up to the operator and may include other antiplatelet or anticoagulation agents not identified.

Table 5: Administration of Anticoagulations and Dual Antiplatelet Medications

Medication	Peri-Procedure (± 24 hours of Index Procedure)	Intra-Procedure	Post-Procedure

Aspirin	Minimum loading dose of 75 mg required, if not on long-term aspirin therapy	N/A	A minimum of 75 mg per day indefinitely
Clopidogrel* **(or similar antiplatelet agent or alternative agent per investigator discretion)**	Minimum loading dose of 300-600 mg required, if not on long-term clopidogrel therapy	N/A	Clopidogrel 75 mg per day for a minimum of 3 years (or per prescribing dose if other similar antiplatelet agent or alternative agent per investigator discretion)
Heparin / Bivalirudin	N/A	Maintain anticoagulation per hospital / institution standard of care (minimum of ACT >250 sec recommended)	N/A

* *For patients requiring anticoagulation therapy (NOAC or OAC), antiplatelet monotherapy with either aspirin or clopidogrel for 3 years, followed by aspirin therapy or other anti-coagulant indefinitely is recommended, using investigator discretion for the best interest and safety of the subject.*

4.9.6 Procedural Evaluation

Final eligibility will be determined based on imaging study and sheath placement. Information on the lesion being treated and the specific vasculature used in its treatment will be collected. The procedural evaluation will consist of the following:

- Lesion characteristics (lesion length and TASC II classification)
- Procedure start and finish times
- Access sites used
- Number of attempts to create each anastomosis
- Complications or adverse events
- Review of angiographic inclusion/exclusion criteria

4.9.7 Discharge Evaluation

The discharge evaluation will consist of:

- Physical examination and health status
- Complications or adverse events
- Anticoagulations and Dual Antiplatelet Medications

4.9.8 Follow-Up Evaluations

Subjects will return to the study center for follow-up evaluations at 1 month (30 days ±7 days), 6 months (180 days ±30 days), 12 months (360 days ±30days), 24 months (720 days ±60 days), and 36 months (1080 days ±60 days) post-index procedure. Follow-up evaluations will include:

- Physical examination and health status
- Rutherford score
- Ankle-Brachial Index/Toe-Brachial Index
- Venous Clinical Severity Score
- Villalta Scale
- Arterial and Venous duplex-ultrasound assessment
- EQ-5D-5L QOL Survey (Baseline, 1 and 12 months)
- VascuQOL Survery (Baseline, 1 and 12 months)
- SF-12 (Baseline, 1 and 12 months)
- 6-minute Walk Test (Baseline, 1 and 12 months,sub-group of subjects only)
- Stent Graft X-ray (12 months)
- Complications and adverse events
- Anticoagulations and Dual Antiplatelet Medications

4.9.9 Subject Lost to Follow-Up

A subject will be considered lost to follow-up and terminated from the study when all of the following criteria have been met:

- On the final study visit with supporting documentation of three unsuccessful attempts on three different days over a period of three (3) months at both study visits by the Investigator or his/her designee to contact the subject or next of kin, one of which should be by certified mail with signature confirmation.
- Prior agreement of the Sponsor to remove the subject from the clinical investigation.

5.0 ASSESSMENT OF EFFICACY

5.1 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is defined as primary patency at 12 months as evidenced by a peak systolic velocity ratio (PSVR) ≤2.5 from DUS and no clinically-driven re-intervention within the stented segment.

The primary effectiveness endpoint hypotheses are:

- H0: 12-month success rate of the PQ Bypass System ≤60.4.0%
- HA: 12-month success rate of the PQ Bypass System >60.4.0%

Based on a PG of 60.4%, a sample size of 202 with 181 subjects with evaluable data at 12 months would provide 91% power to test the primary effective hypothesis at the one-sided alpha level of 0.025, if the PQ Bypass Stent Graft success rate is at least 72%. The Exact Test Method and commercial software PASS14 was used to determine the sample size.

In order to ensure sufficient subjects are available at 12 months for assessment of the primary effectiveness endpoint (i.e., to account for missing data), an additional 21 subjects (approximately 10% estimated attrition rate) may be enrolled, making the total study sample size equal to 202 subjects.

To meet the primary effectiveness endpoint of the IDE Study with a sample size of 202 enrolled and 191 evaluable subjects with 12 month primary patency data, at least 124 subjects (≥68.1%) must experience 12-month primary patency (calculated using the exact confidence interval).

6.0 ASSESSMENT OF SAFETY

6.1 PRIMARY SAFETY ENDPOINT

The primary safety endpoint of the PQ Bypass Detour II IDE Study Freedom from a major adverse event (MAE) at 30 days post-procedure defined as any occurrence of the following events: Death, Clinically-Driven Target Lesion Revascularization (CD-TLR), Amputation of the Treated Limb, Symptomatic Deep Vein Thrombosis (DVT), Pulmonary Embolism, or procedure-related bleeding requiring any transfusion of packed red blood cells or surgery.

7.0 STATISTICS

7.1 STATISTICAL HYPOTHESES AND SAMPLE SIZE JUSTIFICATION

This is a prospective, single-arm, multi-center, international clinical investigation to evaluate the safety and effectiveness of the PQ Bypass System, delivery guidewires, and implant stent grafts for percutaneous

femoropoliteal bypass compared to Performance Goals (PG). There are two hypotheses for the study. One is for the primary effectiveness endpoint – primary patency within 12 months, and one is for the primary safety endpoint – freedom from major adverse events (MAE) through 30 days.

7.1.1. Primary Effectiveness

The primary effectiveness endpoint is defined as primary patency at 12 months as evidenced by a peak systolic velocity ratio (PSVR) ≤2.5 from DUS and no clinically-driven re-intervention within the stented segment.

The primary effectiveness endpoint hypotheses are:

- H0: 12-month success rate of the PQ Bypass System ≤60.4%
- HA: 12-month success rate of the PQ Bypass System >60.4%

Based on a PG of 60.4%, a sample size of 202 with 181 subjects having evaluable data at 12 months would provide 91% power to test the primary effective hypothesis at the one-sided alpha level of 0.025, if the "true" PQ Bypass Stent Graft success rate is at least 72%. The Exact Test Method and commercial software PASS14 was used to determine the sample size.

In order to ensure sufficient subjects are available at 12 months for assessment of the primary effectiveness endpoint (i.e., to account for missing data), an additional 21 subjects (approximately 10% estimated attrition rate) may be enrolled, making the total study sample size equal to 202 TASC II D and complex TASC C subjects.

To meet the primary effectiveness endpoint of the IDE Study with a sample size of 202 enrolled and 181 evaluable subjects with 12 month primary patency data, at least 124 subjects (≥68.1%) must experience 12-month primary patency (calculated using the exact confidence interval).

7.1.2. Primary Safety

The primary safety endpoint of the PQ Bypass Detour II IDE Study is the freedom from MAE rate at 30 days following stent graft implantation, and includes:

- Death
- Target lesion revascularization (TLR)
- Amputation of the index limb
- Symptomatic deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Procedure related bleeding requiring any transfusion of packed red blood cells or surgery

The primary safety endpoint hypotheses are:

- H0: 30-day Freedom from MAE rate of the PQ Bypass System ≤84%
- HA: 30-day Freedom from MAE rate of the PQ Bypass System >84%

The rate of freedom from 30-day MAE for the PQ Bypass System is expected to be no less than 92%. Based on a PG of 84% and an estimated 30-day freedom from MAE rate of 92% for the PQ Bypass System, a sample size of 169 evaluable subjects provides 88% power to test the primary safety hypothesis at the one-sided alpha level of 0.025. The Exact Test Method and Commercial software PASS14 was used to determine the sample size. The final sample size is based on the number required to test the primary effectiveness hypothesis (N=181 including attrition). The primary analysis population will include 202 TASC II D and complex TASC C subjects.

To meet the primary safety endpoint of the IDE Study with a sample size of 181 evaluable subjects (the actual number of subjects who are free from MAEs at 30 days MAE can be no less than 163 subjects (≥89.6%).

7.2 ANALYSIS POPULATIONS

Analysis populations include the Intention to Treat (ITT), Modified Intention to Treat (MITT) and Per Protocol Cohorts. The primary analysis will be on the TASC II D and complex C population excluding roll-ins.

7.2.1. Roll-in Cohort

The first two subjects at each U.S. site may be considered a roll-in subject. Roll-in subject will be pre-identified. Baseline characteristics and safety and efficacy outcomes for this cohort

will be reported separately and be purely descriptive. The roll-in cohort will be excluded from hypothesis testing and from the ITT and MITT populations.

7.2.2. Intention to Treat (ITT)

The ITT Cohort includes all subjects enrolled in the IDE Study. The ITT Cohort will be the primary analysis population to determine if the primary safety endpoint was met in the study.

7.2.3. Modified Intention to Treat (MITT)

The MITT Cohort includes only those subjects/lesions where a PQ Bypass System Stent Graft was implanted. The MITT cohort is a subset of the ITT Cohort. The MITT Cohort will be the primary analysis population to determine if the primary effectiveness endpoint was met in the study.

7.2.4. Per Protocol

The per protocol population is a subset of the MITT group which will exclude all subjects with major protocol deviations (e.g., violations of eligibility criteria, or DAPT compliance).

7.3 GENERAL STATISTICAL CONSIDERATIONS

Demographic, baseline clinical and disease characteristics and procedural results will be summarized in tables for both ITT and MITT populations. For continuous variables, the summary will include the number, mean, median, standard deviation, minimum and maximum. Summaries for categorical variables will include the number and percent of subjects in each category. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and the Exact binomial method for categorical variables. Statistical analyses will be performed using SAS for Windows version 9.4 or higher.

DATA CONSIDERATIONS

7.3.1. Missing Data

Subjects free from clinically-driven target lesion revascularization within the stented segment but do not have sufficient follow-up to assess the primary effectiveness endpoint will be treated as having missing data for the primary effectiveness endpoint. To further evaluate the impact of missing data on the primary

effectiveness endpoint, Kaplan-Meier methods, will also be used to estimate the 12-month primary patency rate.

For the primary safety endpoint analysis, the denominator for each parameter in the safety measures will be the number of subjects who had sufficient follow up (at least 23 days for 30-day visit) plus any subjects who had an event prior to the milestone visit.

All subjects will be accounted for in the study report, including the reasons for any subjects exiting the study early.

Every effort will be made to collect all data points contributing to the primary effectiveness endpoint in the study. The sponsor attempts to minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors and study coordinators. In order to further assess the potential impact of missing data on the primary effectiveness endpoint analyses, the following sensitivity analyses will be performed:

- Worst-Case Scenario: Each missing value for the primary effectiveness endpoint will be treated as a failure. If this still results in rejection of the null hypothesis then no further missing data imputation analyses will be performed for the endpoint.
- If the conclusion is not upheld with the worst-case scenario approach, then the multiple imputation method will be used. A logistic regression model will be used and fifteen imputed datasets will be generated.
- Additionally a tipping point analysis will be performed. The proportion of missing values assigned the status of 'failure' will be sequentially increased to identify the point at which the study conclusions change (i.e., the null hypothesis is no longer rejected).

7.3.2. Data Pooling

Poolability analyses will be performed on primary safety and effectiveness endpoint results to determine if subjects enrolled in different regions (U.S. vs. Outside the US, (OUS)) and subjects at different sites can be pooled.

7.3.2.1. Poolability by Region

To determine if region (U.S. vs. OUS) has an effect on primary safety and effectiveness outcomes, a poolability by region analysis will be performed which compares the primary effectiveness and primary safety endpoint results between subjects enrolled in the U.S. vs OUS. Comparisons will be made using Fisher's Exact Test and poolability will be assessed at the 0.15 significance level. If the p-value is non-significant ($p \geq 0.15$) then the regions will be considered poolable. If the differences are significant ($p < 0.15$), then baseline characteristics will be compared between the U.S. and OUS regions. Since this is a single arm study, differences in outcomes could be due to differences in baseline characteristics by region or due to difference in device performance. To better understand the underlying cause of apparent differences, a model will be fit that includes region, as well as any baseline characteristics that differ significantly by region.

7.3.2.2. Site by Site Poolability

To determine if individual sites have an impact on primary safety and effectiveness endpoint results, a site-by-site poolability analysis will be performed. Comparison will be made using Fisher's Exact Test and poolability will be assessed at the 0.15 significance level. If the p-value is non-significant ($p > 0.15$) then site results will be considered poolable. If the p-value is significant ($p \leq 0.15$) then the effect on the site by site comparison in the presence of any baseline characteristics found to be out of balance across sites will be analyzed. Sites having fewer than 5 subjects will be combined into low enrolling pseudo site pool group(s).

7.4 EFFICACY ANALYSES

7.4.1. Primary Effectiveness Analysis

The MITT cohort will be used to evaluate the primary effectiveness endpoint. All subjects in the MITT population that have a clinically-driven re-intervention within the stented segment that occurs within 360 days of the index procedure will be considered a failure for the primary effectiveness endpoint. All subjects free from clinically-driven re-intervention within the

stented segment who meet the definition of stent graft patency with at least 11 months (330 days) of follow-up will be considered successful with respect to the primary effectiveness endpoint. Subjects free from clinically-driven re-intervention within the stented segment but do not have sufficient follow-up to assess the primary effectiveness endpoint will be treated as missing data.

The primary effectiveness hypothesis will be tested by calculating the one-sided 97.5% confidence limit, using the Exact method. If the lower limit exceeds the performance goal of 60.4% the primary effectiveness hypothesis will be met.

7.5 SAFETY ANALYSES

7.5.1. Primary Safety Endpoint Analysis

The primary safety endpoint is evaluated on a per subject basis and will be calculated as the percent of all ITT subjects with sufficient follow-up that are free from all elements of the primary safety endpoint composite at 30 days. The primary safety hypothesis will be tested by calculating the lower one-sided 97.5% confidence limit, using the Exact method, for the rate of freedom from MAEs. If the lower limit exceeds the performance goal of 84%, the primary safety hypothesis will be met.

7.6 SECONDARY ENDPOINTS AND ADDITIONAL ANALYSES

Secondary and additional analyses will also be carried out on subgroups prespecified in the Statistical Analysis Plan (SAP). These analyses will be purely descriptive, no hypotheses will be tested for secondary endpoints or additional analyses.

7.7 FINAL CLINICAL REPORT

A final clinical report will be prepared at the conclusion of the trial. Copies of the final report will be provided to each investigator and to the respective IRBs/ECs.

8.0 SPONSOR RESPONSIBLITIES

As the Sponsor of this clinical study, PQ Bypass has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA) and ISO 14155:2011 (Section 8 – OUS Sites only). In this study, PQ Bypass will have certain direct responsibilities and will delegate other responsibilities to

Independent Contractors. Together, both PQ Bypass and its Independent Contractors will ensure adherence to the sponsor's general duties (21 CFR 812.40; ISO 14155:2011 Section 8), selection of Investigators (21 CFR 812.43; ISO 14155:2011 Section 8.2.1), monitoring (21 CFR 812.46; ISO 14155:2011 Section 8.2.4.2), supplemental applications (21 CFR 812.35 (a) and (b)), record maintenance (21 CFR 812.140 (b)), and report submissions (21 CFR 812.150 (b)).

8.1 GENERAL DUTIES

(21 CFR 812.40; ISO 14155:2011 Section 8)

The Sponsor's general duties consist of submitting the IDE application to FDA, submitting the Investigational Plan to other applicable national regulatory agencies (as applicable), obtaining FDA, other national regulatory (as applicable) and IRB / EC approvals prior to shipping the devices, selecting qualified Investigators, and shipping devices only to those qualified Investigators. As the sponsor, PQ Bypass is also required to obtain signed study agreements, to provide the Investigators with the information necessary to conduct the study and adequate on-site training to conduct the trial, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators, IRBs / ECs, other national regulatory agencies (as applicable), and FDA.

PQ Bypass will be responsible for providing quality data that satisfies federal regulations and informing about serious unanticipated adverse events and deviations from the protocol. Written progress reports and a final report will be prepared in coordination with the Ultrasound, Angiographic and X-Ray Core Laboratories.

8.2 SELECTION OF CLINICAL SITES & INVESTIGATORS

(21 CFR 812.43; ISO 14155:2011 Section 8.2.1)

PQ Bypass will select qualified clinical sites and Investigators who are experienced with percutaneous transluminal angioplasty and peripheral stenting. The Investigator must work with a qualified IRB / EC to oversee the rights, safety and welfare of the study participants. The clinical site must also have an adequate subject population and the appropriate staffing and equipment to meet the requirements of the study protocol and the expected enrollment time frames.

8.3 MONITORING

(21 CFR 812.46; ISO 14155:2011 Section 8.2.4.2)

PQ Bypass or a designate CROto monitor and oversee the conduct of the The DETOUR II Clinical Study. The Sponsor and/or CRO designee will conduct investigational site monitoring to ensure that all Investigators are in compliance with the Protocol and the Investigators' agreements. The Sponsor and/or CRO designee will monitor the sites to ensure that the completed eCRFs are in agreement with the source documentation and other records, and resolve any differences. Periodic phone contacts and site visits will be conducted to ensure that the Protocol is being followed.

For record verification purposes, the clinical monitor and/or authorized Sponsor representative shall be provided access to hospital records, original laboratory data, and other records and data as they relate to the study and as agreed to with the Investigator prior to the initiation of the trial. The Investigator will also make available to the clinical monitor all regulatory documents, all completed eCRFs, informed consent documents, source documentation and other relevant records for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitor during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representative become aware that an Investigator is not complying with the study protocol, the Investigator Agreement, Good Clinical Practices, applicable privacy standards, or any condition of the study imposed by the IRB / EC, the Sponsor or their authorized representative may immediately secure compliance or discontinue further shipments of the study devices. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the Investigator's termination from the study by the Sponsor.

The Sponsor will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the FDA, other national regulatory agencies (as applicable), the Investigators, and to all reviewing IRBs / ECs.

Study close-out visits will be conducted after the final follow-up visit is completed at each site following the resolution of any outstanding data discrepancies and adverse events. The remaining study devices will be the collected and returned to the Sponsor on or before the close out visit. A final study report will be generated and submitted to the Investigator and the appropriate study oversight authorities. Study document retention requirements will be reviewed with each site during the close-out visit.

8.4 INVESTIGATIONAL SITE TERMINATION

The Sponsor reserves the right to terminate an investigational site from the Study for any of the following reasons:

- Failure to obtain Informed Consent.
- Failure to report Serious Adverse Events within 48 hours of knowledge.
- Loss of or unaccountable device inventory.
- Repeated Protocol violations or safety concerns.
- Repeated failure to complete Case Report Forms.
- Failure to enroll an adequate number of subjects

8.5 INFORMED CONSENT & INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC)

(21 CFR Parts 50 & 56; ISO 14155:2011 Section 4)

All subjects must provide written informed consent in accordance with the local clinical site's IRB / EC. A copy of the consent form from each center must be forwarded to the Sponsor for review and approval prior to submitting it to the IRB / EC. Each site must provide the Sponsor with a copy of the clinical site's IRB / EC approval letter and the informed consent. Continuing review (e.g., institutional annual review) approvals for the continuation of the trial at each clinical site must also be forwarded to the Sponsor, as applicable.

All Protected Health Information (PHI) to be collected in the study will be described in the informed consent form, and all study data will be managed in accordance with the Privacy Law (HIPAA) or international privacy regulations (GDPR), as applicable.

8.6 RECORDS & RECORD RETENTION

(21 CRF 812.140 (b) & (d))

The Sponsor and/or their designated CRO will maintain copies of correspondence, data, device shipments, clinical events (AEs, SAEs, MAEs) and supporting documentation and other records and reports related to this clinical study.

The Sponsor, core laboratories and clinical sites will maintain the DETOUR II study records until two (2) years after the final study report is completed, or longer if required by local, national or international regulatory agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

8.7 STUDY REPORTS

(21 CFR 812.150(b))

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

The Sponsor will submit the required FDA reports identified in this section of the regulation. This includes unanticipated serious adverse device effects, withdrawal of IRB / EC or FDA approval, current 6-month Investigators list, annual progress reports, recall information, final reports, investigators that use the device without obtaining informed consent, and significant risk device determinations.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

8.8 SUPPLEMENTAL APPLICATIONS

(21 CFR 812.35)

As appropriate, the Sponsor will submit changes to the study Protocol for national approval and subsequently to the Investigators to obtain IRB / EC approval.

9.0 QUALITY ASSURANCE & ETHICAL STANDARDS

9.1 TRIAL CONDUCT

The trial will be performed in accordance with the relevant parts of the Code of Federal Regulations, ICH Guidelines for Good Clinical Practices, the European Standard ISO 14155:2011 (OUS sites only), the Declaration of Helsinki, and any regional and/or national regulations. As the study Sponsor, PQ Bypass, has the overall responsibility for the conduct of the study, including the assurance that the study is in compliance with these guidelines, standards and requirements.

9.2 INSTITUTIONAL REVIEW BOARDS / ETHICS COMMITTEES

Before any subject can be enrolled in this trial, the IRB or EC for the specific institution must review and approve the protocol and the Informed Consent Form to be used. A subject cannot be asked to sign the Informed Consent Form until the trial has been fully approved by the institution's IRB/EC. A copy of the

study Protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB / EC for written approval. The Sponsor or their designated CRO will require a copy of any IRB/EC correspondence, as well as the final IRB/EC approval letter and the final IRB/EC approved Informed Consent Form and approvals for protocol and ICF revisions on amendments from each IRB/EC before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB / EC as well as the FDA, for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB / EC of deviations from the protocol or SAEs and UADEs occurring at the site and other SAE/UADE reports received from PQ Bypass in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB / EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB / EC continuance of approval must be sent to PQ Bypass.

9.3 INFORMED CONSENT

A sample Informed Consent form template shall be provided to the Investigator to use to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The reviewing IRB / EC and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the FDA Regulations, GCP guidelines, Declaration of Helsinki, and ISO Standards (OUS sites only).

Prior to participation in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to read the consent, ask questions, and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the subject's dated signature. The subject will receive a copy of the Informed Consent form.

9.4 PROTOCOL AMENDMENTS

An Investigator may not make changes to this protocol without prior approval by the Sponsor. All significant changes to the protocol that may affect the following must be submitted and approved by the FDA before initiating the change:

- Validity of the data or information resulting from the completion of the approved protocol.
- Relationship of the likely subject risk to benefit relied upon to approve the protocol.
- Scientific soundness of the investigational plan.
- Rights, safety, or welfare of the human subjects involved in the investigation.

Any such change to the protocol must be approved by the FDA and submitted and subsequently approved by the site IRB / EC. PQ Bypass will submit a copy of the protocol amendment to all Investigators for their IRBs / ECs to review and ensure the study continues to be conducted consistently across all sites. The investigative sites must send PQ Bypass a copy of the IRB / EC approval letter for the protocol amendment.

PQ Bypass may make certain administrative changes to the protocol without prior approval of the FDA or IRB / EC. PQ Bypass will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites. The site IRBs / ECs will be notified of these changes.

9.5 EMERGENCY ACTIONS

PQ Bypass accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study subject. The Investigator must give notice of any emergency deviations and justification for the deviation to PQ Bypass and the IRB / EC as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

Emergency Use of the investigational device is not permitted in this study.

9.6 DEVIATIONS FROM THE INVESTIGATIONAL PLAN

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol.

Investigators shall be required to obtain prior approval from PQ Bypass before knowingly deviating from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and

Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Deviations must be reported to PQ Bypass regardless of whether medically justifiable, pre-approved by PQ Bypass or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to PQ Bypass. Investigators will also adhere to procedures for reporting study deviations to their EC and CA, where required, in accordance with their specific reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. For reporting purposes, PQ Bypass classifies study deviations as major and minor:

> *Major deviation*: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures, SAE/MAE reporting, device accountability discrepancies, or unauthorized device use.
>
> *Minor deviation*: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc. Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the protocol.

9.7 INVESTIGATOR & STAFF TRAINING

To ensure accurate, complete and reliable data, the Sponsor or its representatives will provide instructional material to the sites, as appropriate; instruct the investigators and study personnel on the protocol, the completion of the CRFs, and study procedures; communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic monitoring visits to the site. During those visits, the Sponsor or its representatives will monitor the subject data recorded in the CRFs against the source documents at the site.

All participating investigators will be trained in the use of the PQ Bypass System prior to participating in the study. PQ Bypass System training will be conducted by the Sponsor or its representatives. All device training will be documented in a training log that will be maintained in the site regulatory binder.

Procedural technique and experience with the PQ Bypass investigational devices may be assessed by clinical/engineering personnel. Observations during the cases will also be discussed with the Investigator and study staff.

9.8 AUDITS AND INSPECTIONS

The principal investigator will also allow representatives of the governing IRB or EC, the U.S. Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all study records, CRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the trial. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the CRFs and compliance with FDA or other regulatory agency regulations.

The principal investigator will inform the Sponsor or the Sponsor's designee should they be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e., Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits, if any.

9.9 MONITORING PROCEDURES

Monitoring visits to the clinical sites will be made periodically during the study, to ensure that all aspects of the current, approved protocol/amendment(s) are followed. Original source documents shall be reviewed for verification of data in the electronic database according to the defined monitoring plan. The Investigator/institution shall make all attempts to grant direct access to original source documents by PQ Bypass personnel, their designees, and appropriate regulatory authorities. It is recognized that all participating institutions may not have procedures for providing access to electronic health records to non-institutional employees. In such situations, the Sponsor and/or designee shall

collaborate with the investigator and institution to ensure alternative access to the complete medical record for enrolled subjects. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

Site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the trial. Clinical monitoring will include a verification that Informed Consent was properly obtained for all enrolled trial participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the eCRFs are in agreement with the source documentation and other records. The investigator will make available to the clinical monitor for review all Informed Consent documents, Internet access to completed eCRFs, source documentation, original laboratory data and other relevant records for all enrolled subjects at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If a deficiency is noted during an on-site visit (or at any other time during the course of the trial), the clinical monitor is required to discuss the situation with the investigator and the Sponsor (if required) to secure compliance.

9.10 INVESTIGATIONAL DEVICE DISTRIBUTION AND ACCOUNTABILITY

9.10.1. INVESTIGATIONAL DEVICE DISTRIBUTION

PQ Bypass will control the distribution of the investigational devices. Each investigational site will be responsible for ordering the investigational devices for the study. The Investigator is responsible for ensuring that the devices are ordered for shipment to arrive at the hospital before the procedure date. Devices will be shipped with an Investigational Device Shipment Record. This form is to be used by PQ Bypass, or distribution designee, and the investigational site to record any shipments of the investigational device. A copy is to be retained by the shipper and the recipient.

9.10.2. DEVICE ACCOUNTABILITY

The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the study. The Investigator shall document in CRFs the lot numbers of the devices used during a case. In addition, the Investigator shall keep complete and accurate records of all devices used or unused that have been returned to PQ Bypass in a Device Accountability Log provided by PQ Bypass.

9.11 RETURN OF DEVICES

All unused investigational devices will be returned to the study Sponsor upon completion of the clinical study. All used investigational devices will be properly disposed of, per institutional procedures. Any investigational device that fails to perform correctly will be returned to the study Sponsor for analysis. The Investigator or his/her designated representative is responsible for device accountability and disposition of all used and unused devices. The study Sponsor or its designated representative will conduct device reconciliation at the completion of subject enrollment or at the conclusion of the study.

IMPORTANT: Please note that the devices must be labeled with a "BIOHAZARD" sticker if there is reasonable belief that the device has come in contact with blood or infectious substances that are known or are believed to cause disease in animals or humans.

9.12 CENTRAL CORE LABS – ANGIOGRAPHY, DUPLEX ULTRASOUND AND X-RAY

In order to ensure that the clinical data and images are analyzed in a controlled, non-biased manner and that the results are analyzed using a standardized process, all angiograms, duplex ultrasound studies and X-rays obtained during this study per study requirements will be submitted to central core labs for analysis.

The core labs will be responsible for analyzing the angiograms and ultrasound images according to the study eligibility criteria, the study endpoints and this study protocol. In addition, they will provide feedback to the sites and Sponsor regarding the quality of the tracings and images. The X-ray core lab will be assessing for stent fracture at the applicable

study time points. Final written summary reports of all angiograms, X-rays, and duplex ultrasounds will be provided to the study Sponsor.

9.13 COVERAGE OF EXPENSES

The treated subjects may receive nominal compensation for participating in the study and may be reimbursed for study specific out-of-pocket expenses (e.g., parking, lodging, etc) and subject to approval by Sponsor and/or IRB/EC.

9.14 CONFIDENTIALITY

Confidentiality of subjects will be maintained throughout the trial. A unique identification code will be assigned to each subject participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor will make every reasonable effort to protect the confidentiality of all subjects participating in the trial.

10.0 INVESTIGATOR RESPONSIBILITIES, RECORDS & REPORTS

The Investigators are responsible for signing the Investigator Agreement prior to the commencement of the study and for ensuring that this trial is conducted according to this study Protocol, GCPs, Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2011 (Section 9 – OUS Sites only) and any other local, national or IRB / EC requirements that apply to Clinical Investigations at their center.

It is also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this study have the appropriate qualifications and that they complete training on the protocol, investigational devices and study procedures, and that subject confidentiality is respected.

10.1 INFORMED CONSENT & INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE

(21 CFR Parts 50 & 56; ISO 15144:2011 Section 4)

Because this study is collecting medical data from subjects providing written informed consent, the Investigator at each site is responsible for securing IRB / EC approval for this study protocol and the Informed Consent documents. The local IRB / EC for each specific institution must review and approve this study protocol and the specific Informed Consent form to be used at that site prior to enrollment of the first subject. The Sponsor must also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a

copy of any IRB / EC correspondence as well as the final approval letter and the final approved Informed Consent from each IRB / EC.

The Investigator is responsible for ensuring that all applicable local and national (21 CFR Part 50, ISO 14155:2011 – OUS sites only) requirements, and Declaration of Helsinki are met when completing the informed consent process. Written, informed consent is to be obtained for all subjects prior to enrollment.

The Investigator or clinical site staff will not make amendments to this Protocol or the Informed Consent form without PRIOR written approval from the Sponsor. All approved amendments must then be submitted to the local IRB / EC and national authorities, as appropriate for approval.

10.2 WITHDRAWAL OF APPROVAL

If the Investigator's IRB or EC withdraws their approval to conduct this study for any reason, the Investigator must notify the Sponsor as soon as possible, but in no event later than five working days after the withdrawal of the approval.

10.3 DEVICE ACCOUNTABILITY

The Sponsor will ship investigational devices to the designated Investigators participating in this study following IRB / EC approval. All Investigators will be responsible for providing a secure storage location for the devices, supervising device use, and the disposal and/or return of the devices as instructed by the Sponsor. In addition, all Investigators will maintain records to document the receipt, use and disposition of all devices received by their site intended for this study. The Sponsor and/or designee will also maintain records of all shipments and disposition of the investigational devices. The Sponsor and/or their authorized Contract Research Organization (CRO) will routinely inspect the clinical site inventory records for device accountability at the clinical sites participating in this study.

10.4 DATA HANDLING AND RECORD KEEPING

10.4.1. SERIOUS ADVERSE EVENTS & MAJOR ADVERSE EVENTS

The Investigator will report to the Sponsor by telephone, email, fax, or electronic CRF submission any SAE or MAE as soon as possible (within 24 hours of the Investigator becoming aware of the event or by the end of the next working day). Additionally, SAEs and MAEs should be reported to the IRB / EC, if required per the clinical site guidelines or as directed by the Sponsor. The Adverse Event eCRF is to be completed and submitted to the Sponsor within five (5) working days of the event. The contact

information for reporting SAEs and MAEs is provided in the study contact section of this protocol.

10.4.2. DEVICE MALFUNCTIONS OR FAILURES

The Investigators will report any Device Malfunctions or Failures that occur, to the Sponsor within 24 hours of the Investigator becoming aware of the device malfunction or failure or by the end of the next working day. The report may be made by or within 24 hours via telephone, email or fax. The Investigator or study staff are to return the devices per the Instructions for Use for investigation. The Device Observation eCRF is to be completed and submitted to the Sponsor within five (5) working days of the event. The contact information for reporting Device Performance issues is provided in the study contact section of this protocol.

10.4.3. DEVIATIONS FROM THE INVESTIGATIONAL PLAN

The Investigator must notify the Sponsor of any deviation from the Investigational Plan. The Investigator should also notify the IRB / EC as required per their local requirements or as directed by the Sponsor. This notice must occur as soon as possible, but in no case longer than five (5) working days after the Investigator becomes aware of a major deviation. Major deviations include, but is not limited to, those that involve the informed consent process, the inclusion/exclusion criteria of the study, SAE/MAE reporting, device misuse or device accountability discrepancies, or any deviation that involves or leads to a serious adverse event in a study participant.

10.4.4. SOURCE DOCUMENTS

The Investigator must maintain detailed source documents on all subjects who are enrolled or who undergo screening in the study. Source documents include subject medical records, hospital charts, clinic charts, investigator subject trial files, as well as the results of diagnostic tests (e.g., laboratory tests, hemodynamic studies).

- The following minimum information should be entered into the subject's medical record:
- The date the subject entered the study and the subject number
- The study protocol number and the name of the Sponsor
- The date that Informed Consent was obtained
- Evidence that the subject meet the study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study related subject visits

- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used
- Occurrence and status of any adverse events (AEs)

The date the subject exited the study and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation

10.4.5. CLINICAL DATA COLLECTION

Standardized electronic case report forms (eCRF) will be used to collect complete and accurate records of the clinical data from the DETOUR II trial according to the GCPs requirements. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study and submitting it to the Sponsor in a timely manner.

10.4.6. INVESTIGATOR FINAL REPORT

The Investigator will report information and events according to the timelines in the Table 6. Within three (3) months of Study completion, the Investigator will provide a final study report that summarizes their enrollment and study participation. This report should include a summary of enrollment, AEs, MAEs, SAEs, UADEs and Device Malfunctions and Failures. This report will be forwarded to the IRB / EC and the Sponsor after all of the enrolled subjects have completed their final follow-up visit or have exited the study and the study close-out visit has been completed, but no later than three (3) months following completion of the last follow-up visit.

Table 6: Investigator Reporting Timelines

Form/Report	Submission Timeframe
Enrollment notification	Completion of Enrollment eCRF within 24 hours of enrollment, or by the end of the next working day.
Electronic CRFs	Completion within 3 working days of study visit.
Angiographic, X-Ray and Duplex Ultrasound Images	Submit to Core Lab within 3 working days of completion.
Adverse Events (non-serious)	Complete eCRF within 14 days of the Investigator becoming aware of the event.
SAEs & MAEs	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local IRB / EC as required or as directed by the Sponsor.
Study Progress Reports	As required by the local IRB / EC (minimum annually).
Final Report to the IRB / EC	Within 3 months of Study completion.

11.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The occurrence of Adverse Events will be monitored during this study. All Adverse Events will be collected through 12 month follow-up and recorded on the Adverse Event eCRF at onset and at each follow-up visit until resolved. SAEs, MAEs and UADEs will be collected for the duration of the study. All device- and procedure-related events, all target limb related events, and all potential non-serious events related to study requirement medications shall be reported throughout the trial.

Potential adverse events associated with use of the PQ Bypass System include, but are not limited to the following:

• Access vessel (arterial / venous) occlusion • Amputation • Aneurysm or pseudoaneurysm • Arteriovenous (AV) fistula • Bleeding complications • Death • Device or deployment malfunction / failure • Drug reactions to antiplatelet agents or contrast medium • Embolism (peripheral or pulmonary) • Fever in absence of infection • Hemorrhage or hematoma • Hypotension/hypertension • Infection local or systemic including bacteremia or septicemia • Malapposition or migration	• Malposition • Myocardial infarction • Pain (insertion site, leg and/or foot) • Renal insufficiency or failure secondary to contrast medium • Shock • Side branch vessel occlusion • Stenosis or occlusion • Stroke or transient ischemic attack • Thrombosis • Vessel wall trauma (dissection, perforation or rupture) • Vessel spasm • Venous flow disruption (deep vein thrombosis, phlebitis, leg swelling and/or development of varicose veins) • Worsening claudication

11.1 ADVERSE EVENTS

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. This includes events related to the study device or events related to the procedures involved.

Adverse Device Effect: An adverse event related to the use of a medical device, including adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation or operation, or any malfunction of the medical device or any event resulting from user error or intentional misuse of the medical device.

The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The following categories of adverse event severity are to be used:

- **Mild**: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no clinical sequelae.
- **Moderate**: Interferes with the subject's usual activity.
- **Serious**: Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes any permanently disabling event.

AEs, SAEs and endpoint events will also be classified as to their relationship to the study device and the study procedure as follows:

- **Definitely Related**: The adverse event is directly and clearly related to the investigational device or procedure.
- **Probably Related**: The exact relationship cannot be determined, but it is most likely that the adverse event and the investigational device or procedure are related.
- **Possibly Related**: The exact relationship cannot be determined, but there is a reasonable likelihood that the adverse event and the investigational device or procedure may be related.
- **Not Related**: The adverse event does not have any identified or perceived relationship to the investigational device or procedure.
- **Unknown**: The relationship of the AE to the device or procedure cannot be determined.

Pre-existing medical conditions or a repeat of symptoms reported prior to the PQ Bypass System procedure will not be recorded as an adverse event. Pre-existing conditions that worsen during a study are considered adverse events.

11.2 SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is any problem or unwanted event encountered in a clinical trial or a performance evaluation that has led, or could have led, directly or indirectly to death or to a serious deterioration in the health of a subject or user or any other person, without regard to whether the event was caused by a medical product. The following events (including laboratory results and outcome events) will be considered to be SAEs and must be reported within 24 hours or by the end of the next business day be reported to the study Sponsor. These

events must be reported whether or not the Investigator believes they are related to study procedures, activities or device:

- Death
- Serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization,
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
    - led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Serious Adverse Device Effect: An adverse device effect that has resulted in any of the consequences of a Serious Adverse Event.

Note: Planned hospitalization for a pre-existing condition, a condition unrelated to the treatment or a procedure required by this study, that is without serious deterioration in health, is not considered a serious adverse event.

11.3 UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

An unanticipated adverse device effects is 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 protocol, investigator's brochure, labeling or published literature, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects.

11.4 ADVERSE EVENT REPORTING

All adverse events will be captured through the 12-month visit as a part of this clinical study. Following the 12-month visit, only SAEs, MAEs, and UADEs will be collected and reportedfor the duration of the study. All device- and procedure-related events and all target limb related events shall be reported throughout the trial. At each contact with the subject, the investigator will seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on

all adverse device effects will be recorded immediately in the source document, and also in the appropriate electronic case report form (eCRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source documents. All SAEs, UADEs, MAEs and possible serious device and/or procedure-related adverse events must be reported by the Investigator (or his/her designee) within 24 hours of becoming aware of the event or by the end of the next business day. The report should include: severity, duration, action taken, treatment outcome and relationship to the adverse event to the study device, procedure, anticoagulations and dual antiplatelet Medications, etc. (i.e., unrelated, relation or relationship unknown).

In the case of serious adverse events (SAE), major adverse events (MAE), procedure and/or device failures and malfunctions, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to PQ Bypass or its designee, if requested. If appropriate, PQ Bypass shall inform the Competent Authority and the relevant Ethics Committee about the event within the appropriate timelines. In accordance with MEDDEV 2.7 / 3 rev.3 (May 2015), the sponsor must report:

- all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it,
- to the National Competent Authorities where the clinical investigation has commenced,
- immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

11.5 REPORTING OF DEVICE FAILURES AND MALFUNCTIONS

All reported device malfunctions or failures of the PQ Bypass System are required to be documented in the eCRF within 24 hours. Device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device will be provided.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from

a device failure or malfunction, that specific event would be recorded in the usual way.

12.0 CLINICAL EVENTS COMMITTEE

An independent Clinical Events Committee (CEC) will be responsible for a systematic review and the adjudication of all major adverse events including, but not limited to, death, major amputations, clinically-driven target lesion revascularization, symptomatic deep vein thromboses. In the case of an MAE with associated imaging, the CEC may review imaging assessments to assess a reported event.

At a minimum, the CEC shall consist of at least three (3) independent physicians, with experience in interventional peripheral endovascular procedures. In order to enhance objectivity and reduce the potential for bias, the CEC members will not have scientific, financial or other conflicts of interest related to the Sponsor or the study investigators or the investigational sites. The CEC will operate and conduct all meetings and event reviews independent of the Sponsor unless specific expert knowledge regarding the characteristics or the function of study device is requested by the CEC from the Sponsor.

The CEC will will meet throughout the study to adjudicate events in an ongoing fashion. The adjudication process, event definitions and required source documentation materials for each type of event will be pre-specified in the CEC charter. All adjudication decisions will be made by the CEC in an independent fashion based upon the review of all available medical evidence associated with each event.

13.0 DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will be responsible for the oversight and safety monitoring of the study. Throughout the duration of the study, the DSMB will review accumulating safety data to monitor for the incidence of serious adverse events that would warrant modification or termination of the study according to pre-specified safety monitoring plan. Any recommendations for study modification or termination prompted by concerns of subject safety, issues related to data monitoring or quality control will be submitted in writing to the Sponsor for consideration and final decision. However, if the DSMB at any time determines that a potential serious risk exists to subjects in the study, the DSMB chairman will immediately notify the Sponsor.

The DSMB will meet at regular intervals through study enrollment to review safety data. DSMB responsibilities, membership, meeting frequencies and procedures will be outlined in the DSMB charter.

14.0 PUBLICATION POLICY

PQ Bypass intends to submit the results of the primary and secondary endpoints for publication within 12 months of completion of the 12-month follow up. Publication will be pursued whether the 12-month outcomes are positive or negative or early termination of the study. The publications policy for this Study is as follows. Following the earliest of a) publication of the multi-center Study results, b) receipt of a notice from PQ Bypass stating that the multi-center Study has been terminated or, c) twenty-four (24) months after completion or termination of the Study at all Investigative sites, Investigators shall have the right to publish, in appropriate scientific journals or other professional publications, information and data collected or produced as a result of their participation in the Study, provided that drafts of the publications have been delivered to PQ Bypass for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release, to which Investigating Parties shall give due consideration. PQ Bypass shall return comments to the Investigator within forty-five (45) days receipt of the draft. In addition, the Investigator shall delay any proposed publication/presentation in the event PQ Bypass so requests to enable PQ Bypass to secure patent or other proprietary protection. In all such publications, credit shall be given to PQ Bypass for its sponsorship of the Study. Similarly, in publications by PQ Bypass regarding the Study, appropriate recognition will be given of the contribution made by the Institution and Principal Investigator, as applicable. PQ Bypass may use, refer to, and disseminate reprints of scientific, medical, and other published articles relating to the Study, including such reprints that disclose the name of Investigators and/or Institution.

A description of this clinical trial is available on http://www.ClinicalTrials.gov. The ClinicalTrials.gov identifier is NCT03119233.

15.0 STUDY DEFINITIONS

Access Site Hemorrhage: Bleeding from the access site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management. Hemorrhage needing ≥ 2 unit RBCs will be considered a serious adverse event.

Access Site Infection: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

Acute Limb Ischemia: Results from a sudden decrease in limb perfusion, usually producing new or worsening signs and symptoms, and often threatening limb viability.

Acute Renal Failure: Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.0 mg/dl; (b) a new requirement for dialysis.

Allergic Reaction: An allergic reaction characterized by rash, upper respiratory congestion, urticaria, shortness-of-breath, or general collapse (anaphylaxis).

Amputation:

Major: any requirement for amputation of the target limb above the ankle.

Minor: any unplanned requirement for amputation of the of the target limb below the ankle.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 26%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Angina, unstable: Angina that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Ankle Brachial Index (ABI): The ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery. It is used to predict the severity of peripheral arterial disease (PAD). ABIs >0.9-1.2 = normal, ≤ 0.9 = peripheral arterial disease, < 0.4 = severe peripheral arterial disease (ischemic pain and ulceration). ABI > 1.2 is likely due to incompressible arteries and is commonly observed in association with long-standing diabetes mellitus, extreme old age, or calcinosis.

Instructions for ABI Calculations:

Obtain systolic blood pressures (SBP) for both arms (brachials) and both ankles [posterior tibials (PT) & dorsalis pedals (DP)].

Divide the higher of the two SBPs for each leg (highest between the PT and DP) by the higher of the two arm pressures to get the right and left ABIs.

Arterial Occlusion / Thrombosis at Groin Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting antegrade flow to the distal limb.

Arterial Perforation/Rupture/Puncture of an Arterial Wall: Classified as follows:

Angiographic perforation: Perforation detected by the clinical site at any point during the procedure.

Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, limb ischemia or death.

Arterial Pseudoaneurysm: Disruption of arterial wall confirmed by imaging study and requiring intervention.

Arteriovenous Fistula (AVF): An abnormal passage or communication between an artery and a vein which may be due to the percutaneous introduction of ancillary devices (e.g., needles, catheters, guide wires) confirmed by imaging studies.

Bleeding Complication (Major): Bleeding resulting in ≥3 g/dl decrease in hemoglobin (if hemoglobin level not available, a decrease in hematocrit of ≥ 10%), or necessitating transfusion of ≥ 2 unit of PRBC's /whole blood, or necessitates surgery/endoscopic intervention.

Access site: Bleeding from the arteriotomy site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management.

Cardiac Arrhythmia: Electrical disruption of the heart rhythm requiring specific medication, DC shock, or pacemaker insertion to address condition.

Cardiogenic Shock: Subject presents with SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous vasopressor agent or an intra-aortic balloon pump (IABP).

Cerebral Vascular Accident (CVA): See Stroke.

Classification of Lesion Morphology (TASC II)

TASC II type A lesions:

Single stenosis ≤ 10 cm in length

Single occlusion ≤ 5 cm in length

TASC II type B lesions:

Multiple lesions (stenosis or occlusions), each ≤ 5 cm

Single stenosis or occlusion ≤ 15 cm not involving the infrageniculate popliteal artery

Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass

Heavily calcified occlusions ≤ 5 cm in length

Single popliteal stenosis

TASC II type C lesions:

Multiple stenosis or occlusions totaling > 15 cm, with or without heavy calcification

Recurrent stenosis or occlusions that need treatment after two endovascular interventions

Complex type C lesions are lesion lengths ≥ 24 cm with a chronic total occlusion or in-stent restenosis

TASC II type D lesions:

Chronic total occlusion of the common or superficial femoral arteries (> 20 cm, involving the popliteal artery)

Chronic total occlusion of the popliteal artery and proximal trifurcation vessels

Closure, Abrupt: Occurrence of new (during the index procedure), persistent slow, reduced, or loss of flow within the target vessel that requires intervention other than the index or adjunct treatment. Abrupt closure may also be referred to as acute occlusion if there is a total loss of flow.

Closure, Late: Target lesion site occlusion that occurs greater than 30 days after the index procedure is completed (e.g., the subject has left the treatment area).

Closure, Subacute: Target lesion site occlusion that occurs after the index procedure is completed (e.g., the subject has left the treatment area) and within 30 days of procedure.

Contrast-Induced Nephropathy: Associated with contrast agent resulting in > 25% increase in serum creatinine or an absolute value of > 0.5 mg/dl.

Contrast Media Reaction: An allergic reaction, immediate or delayed, associated with the intravascular administration of contrast media that results in symptoms (e.g. itching, hives) or physiologic changes requiring treatment (e.g. anaphylactic reaction) or death.

Critical Limb Ischemia (CLI): Clinical manifestation of peripheral arterial disease characterized by Rutherford Clinical Scale Category of 4-6. For the purposes of this study, only subjects with Rutherford Clinical Scale Category of 3, 4 and 5, are eligible for enrollment.

Death: Death is divided into 2 categories:

- ***Cardiovascular death*** is defined as death due to any of the following:
  - Acute myocardial infarction.
  - Sudden cardiac death.
  - Death due to heart failure.

- Death due to stroke.
- Death due to other cardiovascular causes (e.g., procedures, hemorrhage, or other cardiovascular causes).
- Death not attributable to any other cause (e.g., undetermined cause of death).

▪ ***Non-cardiovascular death*** is defined as a death not due to cardiovascular causes (as listed above).

Deep Vein Thrombosis (DVT): Thrombosis of a deep vein, as confirmed by imaging study or direct visualization.

Femoropopliteal DVT: DVT involvement limited to the superficial femoral or popliteal veins, with or without distal (e.g., toward foot) DVT involvement, based on duplex ultrasound exam.

Iliofemoral DVT: DVT involvement of the common or external iliac veins or the common femoral vein, with or without distal (e.g., toward foot) DVT involvement, based on duplex ultrasound exam.

De Novo Lesion: An obstructive or occlusive lesion without previous endovascular or surgical intervention

Device Failure: A device that is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance.

Dissection: Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.

Dissection Classifications (National Heart, Lung and Blood Institute – NHLBI)

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D: Spiral shaped filling defect with our without delayed run-off of the contrast material in the antegrade flow.

Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F: Filling defect accompanied by total coronary occlusion.

Embolization, Distal: Any distal emboli confirmed by imaging.

Embolization, Symptomatic: Clinical signs or symptoms of distal emboli detected in the treated limb distal to the treated lesion after the index procedure ***or*** noted angiographically and requiring mechanical or pharmacologic means to improve flow. This includes new abrupt occlusions or filling defects.

Enrollment: Subjects who are consented and meet all the study inclusion criteria and none of the study exclusion criteria and are treated or treatment is attempted with the study device will be considered enrolled into the study. Subjects who do not meet all inclusion and exclusion criteria (e.g., including ability to cross the lesion with a guidewire, target reference vessel diameter, patent tibioperoneal artery in the target limb, etc.) will be considered an angiographic screen failure and will not be followed in the study (no data will be collected on these subjects).

Hematoma: Collection of blood (or its degradation products) that exceeds 8 cm in diameter, requires treatment, or prolongs hospitalization.

Hypertension: Systolic BP >140 mmHg, or diastolic >90 mmHg requiring specific medical therapy.

Hypotension: Any prolonged systolic blood pressure <80 mmHg associated with symptoms and requiring intravenous vasopressor medications.

Infection, access site: Infection at the vascular access site, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Intention to Treat (ITT): The principle of including outcomes of all subjects in the analysis who are enrolled and treated (attempted or completed) into the study, regardless of noncompliance, Protocol deviations, or withdrawal.

Limb Ischemia: Deficient supply of oxygenated blood to the tissues in the limbs that is due to obstruction of the inflow of arterial blood characterized by pain and/or discoloration of the limb and/or tissue loss.

Luminal Patency: Restenosis <50% as determined by angiography or duplex ultrasound.

Major Adverse Event (MAE): An MAE comprises the following: Death, Clinically-Driven Target Lesion Revascularization (CD-TLR), Amputation of the Treated Limb, Symptomatic Deep Vein Thrombosis (DVT), Pulmonary Embolism, or procedure-related bleeding requiring any transfusion of packed red blood cells or surgery.

Major Adverse Limb Events (MALE): A Major Adverse Limb Event (MALE) defined as above-ankle amputation or major reintervention including placement of a new bypass graft, interposition graft, thrombectomy, or thrombolysis.

Myocardial Infarction (MI): Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, requiring a combination of evidence of myocardial necrosis [either changes in cardiac biomarkers (e.g., troponins or CK-MB) or post-mortem pathological findings] and supporting information devired from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

Patency, Primary Vessel: Vessel patency at a given time point will be determined by the absence of clinically-driven target lesion revascularization and absence of recurrent target lesion diameter stenosis > 50% by imaging (e.g., invasive angiography or most commonly, duplex ultrasonography). Luminal diameter is assessed by core lab using angiography or duplex ultrasound imaging. Loss of primary stent patency is deemed when peak systolic velocity ratio (PSVR) is >2.5, or where angiography reveals >50% diameter stenosis, or where the subject undergoes clinically-driven TLR. When both imaging modalities are available, angiography takes precedence.

Patency, Tibioperoneal Run-Off: Subject has at least one patent tibioperoneal run-off vessel with <50% stenosis confirmed by angiography at time of enrollment.

Perforation: Puncture of an arterial wall.

Pseudoaneurysm: Disruption of the arterial wall characterized by an out-pouching or pocket with swirling, flowing blood outside of the confines of the arterial lumen.

Recurrent Occlusion: Occlusion (i.e., total obstruction of vessel lumen) after a successful canalization.

Recurrent Thrombosis: Thrombosis (i.e. sub-total obstruction of vessel lumen) following successful treatment.

Reference Vessel Diameter, Proximal (RVD_{prox}): Diameter of normal vessel immediately proximal to the treated segment.

Reference Vessel Diameter, Distal (RVD_{dist}): Diameter of normal vessel immediately distal to the treated segment.

Renal Failure (Acute): Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.0 mg/dl; (b) a new requirement for dialysis.

Renal Insufficiency: An increase in serum creatinine of ≥ 1.0 mg/dl over previous value requiring medical treatment but which does not require dialysis to resolve.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

Respiratory Insufficiency: Deterioration of subject's respiratory efforts that require supportive or medical treatment.

Restenosis: Reoccurrence of narrowing or blockage or target lesion. Recurrence of ≥ 50% diameter stenosis within 1 cm proximal and/or distal to the target lesion as measured by duplex ultrasound (PSV ≥ 2.5) or angiography (note: in cases where both imaging modalities are available, the angiography will take precedence).

Retroperitoneal Bleed: Bleeding into the back of the abdomen from a vascular access or puncture site.

Rutherford Clinical Category Scale: Clinical scale identifying three grades of claudication and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss.

Category	Clinical Description
0	Asymptomatic

1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Ulceration or gangrene

Stent Fracture: Defined as clear interruption of stent strut observed in a minimum of two projections, determined by core lab examination of X-ray images.

Stent Strut Fracture Types:

Type 0: No strut fractures.

Type I: Single strut fracture only.

Type II: Multiple single strut fractures that can occur at different sites.

Type III: Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments.

Type IV: Multiple strut fractures resulting in displacement of segments of the stent.

Type V: Spiral strut fracture.

Stroke: Any neurological deficit defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. May be further categorized as:

Ischemic Stroke: defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhagic Stroke: defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Target Lesion Revascularization, Clinically-driven (CD-TLR): Clinically-driven target lesion revascularization is defined as target lesion revascularization performed due to target lesion diameter stenosis > 50% AND either evidence of clinical or functional ischemia (e.g., recurrent/progressive intermittent claudication, critical limb ischemia) OR recurrence of the clinical syndrome for which the initial procedure was performed.

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Toe Brachial Index (TBI): A Toe Brachial Index (TBI) is performed when the ABI or Ankle Brachial Index is abnormally high due to plaque and calcification of the arteries in the leg; this is caused by atherosclerosis and is most often found in diabetic patients. The abnormally high ABI is >1.3.

Instructions for TBI Calculations:

Obtain systolic blood pressures (SBP) for both arms (brachials) and both great toes.

Divide the higher of the two SBPs for each leg (highest between the PT and DP) by the great toe pressure to get the right and left TBIs.

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack: A neurological event defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.

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APPENDIX I: INFORMED CONSENT FORM

APPENDIX II: INSTRUCTIONS FOR USE (IFU)