Post-Approval Study of the GORE® VIABAHN® Endoprosthesis for the Treatment of In-Stent Restenosis in the Superficial Femoral Artery

Protocol Number: ISR 14-04

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W. L. Gore and Associates, Inc.
Medical Products Division

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Amendment 1 (Rev. 2)

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PROTOCOL SUMMARY

Study Title	Post-Approval Study of the GORE® VIABAHN® Endoprosthesis for Treatment of In-Stent Restenosis in the Superficial Femoral Artery
Protocol Number	ISR 14-04
IDE or PMA Number	Post approval w/PMA# **P040037 S060**
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 3250 W. Kiltie Lane Telephone: 800-437-8181
Study Device	The GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface (US); GORE® VIABAHN® Endoprosthesis with PROPATEN™ Bioactive Surface (EU); and subsequently referred to as GORE® VIABAHN® Endoprosthesis throughout this protocol.
Study Design	Prospective, multicenter, single-arm study
Study Objective	The objective is to evaluate post-market safety and effectiveness of GORE® VIABAHN® Endoprosthesis for treatment of In-Stent Restenosis of the SFA
Primary Endpoints	Effectiveness Endpoint: Primary Patency at 12 months by Kaplan-Meier analysis Safety Endpoint: Device- and procedure-related Serious Adverse Events within 30 days of the procedure
Secondary Endpoint(s)	• Acute Procedural Success • Primary Patency at 30 days, 12, 24, & 36 months • Primary Assisted Patency at 30 days, 12, 24, & 36 months • Secondary Patency at 30 days, 12, 24, & 36 months • Freedom from TLR at 30 days, 12, 24, & 36 months • Freedom from Major Amputation at 30 days, 12, 24, & 36 months • Change in Ankle-Brachial Index from pre-procedure at 30 days, 12, 24, & 36 months • Change in Rutherford Category from pre-procedure at 30 days, 12, 24, & 36 months • Stent Fracture Assessment at 12, 24, & 36 months
Subject Population	The Subject population will include symptomatic PAD patients (Rutherford 2-5) with occlusive lesion(s) within and adjacent to previously implanted non-covered stent(s) located in the superficial femoral artery
Number of Subjects	108 (minimum 81 (75%) of Subjects in the US) A minimum of 20 Subjects will be enrolled with a lesion length of 230-270 mm.
Number of Sites	A minimum of 15 Sites in the U.S. Up to 5 OUS Sites may be included.
Expected Time to Complete Enrollment	24 months

Schedule of Events	**Screening**: Informed Consent, Medical History, Demographics **Treatment**: Angiographic confirmation of final eligibility, Deployment of study device, Post-procedural angiography, Adverse Events **Follow-up Schedule**: 30 days, 12, 24 and 36 months **Follow-up Assessments:** Adverse events, ABI, Rutherford, X-ray (12, 24, 36 months), Duplex ultrasound
Expected Study Timeline	Study Initiation: SEP 2015 Number of sites with IRB approvals/month: 2 Number of subjects enrolled/month: 0.5/site Enrollment Completion: SEP 2017 Study Follow-Up Completion: SEP 2020 Final Report Submission: Submitted within 3 months of completion of the last patient follow-up

LIST OF ABBREVIATIONS

ABI	Ankle-Brachial Index
AE	Adverse Event
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CDMS	Clinical Data Management System
CE	Conformité Européenne
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
cm	Centimeters
CRF	Case Report Form
CRO	Contract Research Organization
ePTFE	Expanded Polytetrafluoroethylene
EU	European Union
FDA	Food and Drug Administration (United States)
Fr	French (sizing)
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HIT	Heparin-Induced Thrombocytopenia
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board (U.S.)
ISR	In-stent Restenosis
mm	Millimeters
OUS	Outside the United States
PAD	Peripheral Artery Disease
PI	Principal Investigator
PMA	Premarket Approval
PSV	Peak Systolic Velocity
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
TBI	Toe-brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
U.S.	United States

1. Introduction

1.1. Disease

Patients with lifestyle-limiting claudication from atherosclerotic stenosis and occlusion of the Superficial Femoral Artery (SFA) exhibit a decreased quality of life, e.g. pain or cramping in the legs or buttocks upon exertion[1]. Vascular surgeons have traditionally managed claudication conservatively, given the morbidity and mortality associated with surgical bypass procedures[2]. If indicated, interventional techniques and devices provide clinicians with a less invasive alternative to surgery for the treatment of claudication and limb ischemia[3].

Plain Old Balloon Angioplasty (POBA) of the SFA in longer lesion lengths (>10cm) has yielded reported primary patency rates of 22%[4]. Bare metal stents (BMS) have demonstrated better primary patency rates when compared to POBA alone[5]. Still, one-year restenosis rates remain high and continue to plague both therapies (PTA 64% vs BMS 37%) [6].

Similar to coronary stenting, the leading cause of in-stent restenosis (ISR) has been identified as neointimal formation. Implant-induced hyperplasia, endothelial denudation, thrombus reorganization and negative arterial remodeling are factors that contribute to ISR. Characteristics of the originally treated lesion have been shown to predict future occurrence of ISR. Long, diffuse stenotic or occluded lesions treated with BMS commonly become restenotic[7, 8, 9].

1.2. Historical Treatments

The following treatment modalities have been used globally to treat in-stent restenosis of the superficial femoral artery:

- Conventional percutaneous transluminal angioplasty
- Cutting balloon
- Cryoplasty
- Atherectomy
- Re-stenting
- Drug covered balloons
- Drug-eluting stents

The GORE® VIABAHN® Endoprosthesis has been utilized as a treatment option for SFA ISR. The flexibility of the VIABAHN® Endoprosthesis, as exemplified by its low rate of fracture in long lesion lengths, allows it to withstand the mechanical forces of the SFA[10]. Additionally, the ePTFE can provide a physical barrier between the arterial lumen and in-growth from neointimal formation. Since this has been hypothesized to be the failure mechanism of the original stent, it would stand to reason that blocking further neointimal ingrowth via an ePTFE covering would provide a promising treatment strategy.

1.3. Study Device Description

The GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface (marketed as GORE® VIABAHN® Endoprosthesis with PROPATEN™ Bioactive Surface in the EU) is a flexible, self-expanding endoluminal endoprosthesis consisting of two components: 1) a tubular section of ePTFE which has been modified with Heparin Bioactive Surface and 2) an external supporting structure, constructed from nitinol, extending along its entire length.

Table 1: GORE® VIABAHN® Endoprosthesis Configurations and Vessel Sizing Guidelines

Device Sizing		Introducer Sheath Size (Fr)	Introducer Sheath Size (Fr)	Available Device Lengths[1] (cm)	Recommended Balloon Diameter for Device Touch-up (mm)
Labeled Device Diameter (mm)	Recommended Vessel Diameter (mm)	Guidewire Diameter 0.035" (0.889 mm)	Guidewire Diameter 0.018" (0.460 mm)		
5	4.0 – 4.7	7	6	2.5, 5, 10, 15, 25	5.0
6	4.8 – 5.5	7	6	2.5, 5, 10, 15, 25	6.0
7	5.6 – 6.5	8	7	2.5, 5, 10, 15, 25	7.0

[1]Labeled device lengths are nominal.

The U.S. regulatory history for the GORE® VIABAHN® Endoprosthesis is as follows:

The original PMA P040037, GORE® VIABAHN® Endoprosthesis, was approved on June 14, 2005 for improving blood flow in patients with symptomatic peripheral arterial disease in superficial femoral artery lesions with reference vessel diameters ranging from 4.8 to 7.5 mm.

PMA supplement P040037/S003 was approved on April 24, 2007 to add 5mm diameter device configurations and to make associated modifications to the indications to add reference vessel diameters from 4.0 – 4.7mm.

PMA supplement P040037/S004 (GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface) was approved on July 31, 2007 to add device configurations containing a Heparin Bioactive Surface.

PMA supplement P040037/S007 was approved on August 14, 2008 for the addition of an indication for treatment of iliac artery lesions.

PMA supplement P040037/S050 was approved on October 18, 2013 for the addition of a 25cm length for the 5-8mm diameter endoprostheses and where the indication statement was modified to specify lesion lengths.

PMA P130006 was approved on December 5, 2013 for the addition of an indication to treat stenosis or thrombotic occlusion in AV access grafts.

PMA supplement P040037/S060 was approved on September 19, 2014 for an addition of the indication to treat SFA in-stent restenosis.

Currently, the GORE® VIABAHN® Endoprosthesis is approved for the following indications in the US:

The GORE® VIABAHN® Endoprosthesis is indicated for improving blood flow in patients with symptomatic peripheral arterial disease in superficial femoral artery de novo and restenotic lesions up to 270 mm in length with reference vessel diameters ranging from 4.0 – 7.5 mm.

The GORE® VIABAHN® Endoprosthesis is indicated for improving blood flow in patients with symptomatic peripheral arterial disease in superficial femoral artery in-stent restenotic lesions up to 270 mm in length with reference vessel diameters ranging from 4.0 – 6.5 mm.

The GORE® VIABAHN® Endoprosthesis is indicated for improving blood flow in patients with symptomatic peripheral arterial disease in iliac artery lesions up to 80 mm in length with reference vessel diameters ranging from 4.0 – 12 mm.

The GORE® VIABAHN® Endoprosthesis is also indicated for the treatment of stenosis or thrombotic occlusion at the venous anastomosis of synthetic arteriovenous (AV) access grafts.

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2. Study Objectives

2.1. Primary Objective(s)

The primary objective of ISR 14-04 is to evaluate the post-market performance of GORE® VIABAHN® Endoprosthesis for the treatment of in-stent restenosis of the superficial femoral artery in a primarily U.S. population (at least 75% of patients being treated in the U.S.).

3. Study Design

3.1. Description of Study Design

This study is a prospective, multicenter, non-randomized single-arm study to evaluate the post-market performance of the GORE® VIABAHN® Endoprosthesis for the treatment of in-stent restenosis in the superficial femoral artery.

A minimum of 15 Clinical Investigative Sites (referred to as “Sites” in the remainder of this document) in the U.S. and a maximum of 5 OUS Sites will participate in this study.

A total of 108 Subjects (a minimum of 81 Subjects from the U.S. and a maximum of 27 OUS Subjects) will be enrolled in this study with a limit of 30 Subjects per U.S. Site.

A minimum of 20 Subjects (out of the total 108 Subjects) will be enrolled with lesion lengths of 230-270mm. The study will be actively monitored to ensure the minimum enrollment threshold for this long lesion length cohort is met.

The anticipated accrual period is 24 months assuming an accrual rate is approximately 0.5 Subjects per month/Site.

Patients are to be enrolled into the study provided all inclusion and no exclusion criteria are met as specified in Section 4. Subjects will be evaluated through hospital discharge and will be scheduled for follow-up visits at 30 days and at 12, 24 and 36 months post treatment. Accounting for the expected period of enrollment, the total estimated duration of the study is 60 months.

3.2. Study Endpoint(s)

3.2.1. Definitions

Ankle Brachial Index: the ankle systolic pressure in the study limb divided by the highest brachial systolic pressure in either arm

Acute Procedural Success: successful delivery of study device and complete coverage of the target lesion without a procedure or device-related Serious Adverse Event prior to hospital discharge

Major Amputation: removal of the lower limb above the metatarsals in the study limb, resulting from a vascular event

Patency: blood flow through the study device

Primary Patency: patent blood flow through the study device, which requires either a PSVR measurement ≤ 2.5 or patent flow indicated by the Core Lab, and without repeat intervention

Primary Assisted Patency: blood flow through the study device regardless of repeat interventions to maintain patency prior to occlusion

Secondary Patency: blood flow through the study device regardless of repeat interventions to maintain or restore patency after occlusion

Target Lesion(s): stenotic or occluded segment(s) within and adjacent to a previously implanted non-covered stent(s) (>30 days) in the superficial femoral artery. An adjacent lesion is an extension of the stenotic or occluded segment that is contiguous with that lesion within the previously implanted non-covered stent

Target Lesion Revascularization (TLR): repeat intervention within the study device and 5 mm proximal or distal to the edge of the study device to maintain or re-establish patency

Toe Brachial Index: the toe systolic pressure in the study limb divided by the highest brachial systolic pressure in either arm

Stent Integrity: freedom from study device stent fracture which is clearly distinguishable on imaging from the previously implanted non-covered stent

3.2.2. Primary Endpoints

The primary effectiveness endpoint is Primary Patency at 12 months post-procedure. This will be estimated through 365 days along with a 95% confidence interval using Kaplan-Meier analysis.

The primary safety endpoint is procedure or device-related Serious Adverse Events within 30 days of the index procedure. The total number of events as well as the number of Subjects experiencing them will be tabulated along with a 95% confidence interval.

3.2.3. Secondary Endpoints

The secondary endpoints for this study include:

- Acute Procedural Success
- Primary Patency at 30 days, 12, 24 and 36 months
- Primary Assisted at 30 days, 12, 24 and 36 months
- Secondary Patency at 30 days, 12, 24 and 36 months
- Freedom from Target Lesion Revascularization at 30 days, 12, 24 and 36 months
- Freedom from Major Amputation at 30 days, 12, 24 and 36 months
- Change in Ankle-Brachial Index from pre-procedure at 30 days, 12, 24 and 36 months
- Change in Rutherford Category from pre-procedure at 30 days, 12, 24 and 36 months
- Stent Fracture Assessment at 12, 24 and 36 months

4. Study Population

4.1. Description of Population

Patients presenting with ≥ 50% in-stent restenosis and/or an occlusion in a previously implanted non-covered stent(s) located in the superficial femoral artery are eligible for participation in the study. The previously implanted non-covered stent(s) must have been implanted greater than 30 days prior to the index procedure. Eligible patients must present with life-limiting claudication, resting leg pain or minor tissue loss (Rutherford Category 2-5). Patients must be candidates for endovascular treatment.

Patients presenting with the following lesion characteristics are eligible for enrollment:

- Total lesion length of up to 270 mm, consisting of in-stent and adjacent occlusive disease
- Reference vessel diameter between approximately 4.0 and 6.5 mm

The study has been designed with standard eligibility criteria to address any known or foreseeable factors that may compromise the outcome of the study or the interpretation of results. Only patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be enrolled.

4.2. Inclusion Criteria

Potential Subjects must meet all of the following Clinical Inclusion Criteria:

1. Patient is ≥ 18 years old at the time of informed consent signature
2. Patient is willing to give written informed consent
3. Patient has a previously implanted (>30 days) non-covered stent(s) located in the superficial femoral artery
4. Patient has life-style limiting claudication, resting leg pain or minor tissue loss (Rutherford Category 2-5)
5. Patient demonstrates an ABI ≤ 0.9. If ABI > 0.9 or not measureable, patient is eligible for study if toe-brachial index (TBI) is ≤ 0.5
6. Patient is male, infertile female or female of childbearing potential with a negative beta hCG pregnancy test within 7 days of the index procedure
7. Patient is capable of complying with protocol requirements, including follow-up visits

Potential Subjects must meet all of the following Angiographic Inclusion Criteria:

1. Patient has ≥ 50% in-stent restenosis and/or an occlusion in a previously implanted (>30 days) non-covered stent(s) located in the superficial femoral artery defined as beginning at least 1 cm below the origin of the profunda femoris artery and ending at least 1 cm above the intercondylar notch
2. Patient has a maximum total lesion length of 270 mm, consisting of in-stent and adjacent occlusive disease
3. Patient has a minimum of 1 cm of non-stenosed vessel both proximal and distal to the target lesion(s)
4. Patient has a reference vessel diameter between 4.0 and 6.5 mm
5. The guidewire and delivery system must cross the target lesion(s) intraluminally
6. Patient has a patent popliteal artery (<50% stenosis) distal to the target vessel
7. Patient has at least 1 patent infrapopliteal runoff vessel (<50% stenosis) not requiring intervention

8. Angioplasty balloon can be fully expanded in the target lesion during pre-treatment step

4.3. Exclusion Criteria

Potential Subjects will not be eligible for study participation if they meet any of the following Clinical Exclusion Criteria:

1. Patient has a known allergy to stent graft components (nickel-titanium or ePTFE)
2. Patient has known allergy to contrast media that cannot be adequately pre-medicated prior to the study procedure
3. Patient with known hypersensitivity to heparin, including those patients who have had a previous incidence of heparin-induced thrombocytopenia (HIT) type II
4. Patient has a known intolerance to anticoagulation or antiplatelet therapy
5. Patient has an uncorrected bleeding disorder (platelet count <80,000/µL)
6. Patient has any known coagulation disorder, including hypercoagulability
7. Patient has severe chronic renal insufficiency (creatinine level ≥ 2.5mg/dL) within 30 days prior to study procedure unless currently on hemodialysis
8. Patient has septicemia or uncontrolled infection
9. Patient has any planned surgical intervention/procedure within 30 days of the study procedure
10. Patient has major distal amputation (above the transmetatarsals) in the study or non-study limb
11. Patient has prior ipsilateral femoral artery bypass
12. Patient has severe medical comorbidities (untreated CAD/CHF, severe COPD, metastatic malignancy, dementia, etc.) or other medical condition that would preclude compliance with the study protocol or 3-year life expectancy
13. Patient has severe ipsilateral common or deep femoral disease requiring intervention
14. Patient has any previous surgery in the target vessel
15. Patient has had vascular access via the lower extremities within 30 days of the index procedure
16. Patient has had previous target vessel in-stent restenosis treated by relining with another stent
17. Patient is currently participating in another clinical research trial, unless approved by Sponsor

Potential Subjects will not be eligible for study participation if they meet any of the following Angiographic Exclusion Criteria:

1. Patient has untreated flow-limiting aortoiliac stenotic disease
2. Patient has an aneurysm adjacent to the target lesion(s)
3. Patient has perioperative unsuccessful ipsilateral percutaneous vascular procedure to treat inflow prior to enrollment during the index study procedure
4. Patient has femoral or popliteal aneurysm located in the target vessel
5. Patient has non-atherosclerotic disease resulting in occlusion (e.g. embolism, Buerger's disease, vasculitis)
6. Patient has angiographic evidence of intra-arterial thrombus or atheroembolism from inflow treatment
7. Patient has target lesion access not performed by transfemoral approach

5. Study Procedures/Evaluations

Any Site staff performing study-specific duties must be qualified by training and experience and must also be appropriately trained on the study protocol and procedures. Delegation of study-specific duties at each Site must be acknowledged by the Site's Principal Investigator and documented on the Delegation of Authority Log.

5.1. Schedule of Events

Table 3: Schedule of Events

	Pre-Procedure[1]	Procedure	Discharge	Follow-Up Visit		
				30 Days	12, 24 & 36 Months	Unscheduled
Informed Consent	X					
Medical History and Demographics	X					
Height and Weight	X					
CBC	X					
Creatinine, serum	X					
beta-hCG test, if indicated	X within 7 days of study procedure					
ABI/TBI, resting[2]	X		X	X	X	X
Rutherford Classification	X			X	X	X
Anti-Platelet/Anti-Coagulation Therapy Assessment	X		X	X	X	X
Clinical Inclusion/Exclusion	X					
Angiography		X		If indicated	If indicated	If indicated
Angiographic Inclusion/Exclusion		X				
Adverse Events		X	X	X	X	X
X-Ray[3]		X[4]			X	
Duplex Ultrasound[3]				X	X	If indicated

1 Pre-procedure assessments required within 30 days of study procedure unless noted
2 If TBI used to qualify patient for study participation, TBI must be collected throughout duration of all study follow-up intervals.
3 Imaging sent to Core Lab for Assessment
4 Required imaging: X-ray image of non-covered stent(s) prior to deployment of Study Device AND X-ray image of Study Device post-deployment

5.2. Informed Consent Process

All patients must provide informed consent prior to any study related procedures being performed. The case history (i.e., source documents/Subject chart) for each Subject shall document that such informed consent was obtained. The current IRB/EC approved consent form will be signed and personally dated by the Subject, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for their records.

5.3. Pre-Screening/Screening

Patients who appear to meet clinical eligibility criteria via initial screening and review of existing medical records will be scheduled for a clinical evaluation. The informed consent must be signed prior to any study-related activity or procedure. All patients who sign an ICF will be considered entered into the screening phase of the study and should be recorded on the Screening and Enrollment Log.

The clinical evaluation must be performed within 30 days prior to the study procedure, unless noted, and will include:

- Informed consent
- Medical history and demographics
- Height and weight
- CBC
- Creatinine, serum
- b (beta)-hCG pregnancy testing within 7 days of the study procedure, if indicated
- ABI/TBI, resting (Note: If TBI is used to qualify patient for study participation, TBI must be collected throughout duration of all study follow-up intervals)
- Rutherford Classification
- Anti-platelet/anti-coagulation therapy assessment
- Review of clinical inclusion and exclusion criteria

5.4. Enrollment

The patient is considered enrolled when all inclusion criteria and no exclusion criteria have been met (as defined in Section 4.2 & 4.3).

5.5. Procedure

Patients may be admitted the day prior to the procedure for hydration, if deemed medically necessary. Alternatively, Subjects may be admitted the day of the procedure. Antiplatelet medication should be initiated prior to placement of the study device at a dose deemed appropriate by the Investigator.

On the day of the procedure, the patient will be prepped for percutaneous intervention per institutional standards. Ultrasound-guided vascular access is recommended. When possible, a percutaneous Seldinger technique is preferred; however a cut-down may be performed when indicated. The guidewire must cross the target lesion(s) intraluminally. Use of image-centered, magnified-view contrast angiography (including a marker guidewire or catheter) is recommended.

<u>Assessment of Lesion Characteristics</u>

Procedural angiography will be utilized to assess target lesion characteristics and to determine final eligibility for enrollment. Lesion characteristics, including total lesion length, percent stenosis, presence of occlusion and calcification will be recorded. Additionally, target lesion location should be recorded, confirming the presence of in-stent restenosis and noting any adjacent disease (if present).

Assessment of Non-covered Stent
A baseline image of the previously implanted non-covered stent prior to any study treatment is required. This image can be captured during the baseline angiogram (X-ray shot without contrast) or by plain film X-ray. Imaging will be sent to the Core Lab for assessment.

Treatment of Target Lesion and Device Deployment
Prior to study device implantation, pre-dilation of the target lesion is required with full expansion of the balloon within the lesion(s). The margins of the angioplasty treatment should be carefully marked to ensure complete coverage with the study device. The results of the pre-dilation should be evaluated angiographically. Any other pre-treatment procedures prior to balloon angioplasty may be conducted at the discretion of the Investigator.

Study device sizing, introduction, positioning and deployment should be performed in compliance with Instructions for Use (IFU). Refer to **Table 1**, GORE® VIABAHN® Endoprosthesis Configurations and Vessel Sizing Guidelines.

All areas that were pre-dilated should be covered with the study device. In addition, the study device should extend into healthy vessel a minimum of 1 cm proximal and distal to the target lesion(s). If overlapping devices is required to ensure complete coverage, there should be at least 1 cm of overlap between devices and device diameters should not differ by more than 1 mm. Post-dilation should be performed after each study device deployment to ensure seating against the vessel wall.

Procedural Completion Imaging
Final post-procedure angiogram will be performed to assess technical results. A post-procedure image is required. This image can be captured during final angiogram (X-ray shot without contrast) or by plain film X-ray. Imaging will be sent to the Core Lab for assessment.

Approved closure devices may be utilized at the Investigator's discretion. If a closure device is not used, sheath removal will be performed in accordance with institutional standard of care. Adequate hemostasis at the arterial puncture site as determined by the Investigator should be achieved prior to discharge.

Adverse events will be collected from the study procedure forward.

Discharge
Prior to discharge, a resting ABI/TBI will be measured. Discharge anti-platelet/anti-coagulation therapy and any additional adverse events will be documented.

Anti-platelet/Anti-coagulation Therapy

The Subject should be discharged and maintained on anti-platelet/anti-coagulation therapy at a dosage deemed appropriate by the Investigator.

The following medication regime is recommended:

- Dual anti-platelet therapy should be continued for a minimum of 6 months including Clopidogrel 75 mg PO QD (Other members of the thienopyridine class of ADP receptor inhibitors may be prescribed in place of Clopidogrel if subject intolerant to Clopidogrel) and Aspirin 81 – 325 mg PO QD
- Aspirin 81 – 325 mg PO QD should be continued through study follow-up

5.6. Repeat Interventions

In some Subjects, a repeat intervention may be required following the index procedure. Investigators should use standard of care at their institution for performing repeat interventions. An angiogram of the study lesion both pre- and post-intervention should be taken and recorded on the appropriate CRFs. All commercially available sizes of the GORE® VIABAHN® Endoprosthesis may be used for repeat interventions.

Angiography performed without subsequent intervention to maintain or re-establish patency is not considered a repeat intervention.

5.7. Follow-Up

All Subjects are required to return to the Investigator for follow-up evaluations at 30 days, 12, 24 and 36 months after the index procedure. The schedule of events is outlined in **Table 3**.

Follow-up visits will be scheduled at appointed times after the date of index procedure. The Sponsor recognizes that Subjects may not be able to return for follow-up visits on the exact date required. Thus, a period during which each visit is allowed (window) is presented in **Table** 4.

Table 4 Study Visit Windows

Follow-up Visit	*Window*
30 days	30 ± 7 days
12 months	365 ± 45 days
24 months	730 ± 45 days
36 months	1095 ± 45 days

The following data are required and will be collected at 30 days post-procedure:

- ABI/TBI, resting
- Rutherford Classification
- Anti-platelet/Anti-coagulant therapy assessment
- Adverse Events
- Duplex Ultrasound

The following data are required and will be collected at 12, 24 and 36 months post-procedure:

- ABI/TBI, resting
- Rutherford Classification
- Anti-platelet/Anti-coagulant therapy assessment
- Adverse Events

- X-ray
- Duplex Ultrasound

The following data is required and will be collected at any Unscheduled Study-Related Visit or

- ABI/TBI, resting
- Rutherford Classification
- Anti-platelet/Anti-coagulant therapy assessment
- Angiography, if indicated
- Adverse Events
- Duplex Ultrasound, if indicated

5.8. Subject Withdrawal from the Study

It is important that the Investigator encourage Subjects to return for all required follow-up visits. A Subject may withdraw from the study at any time and should notify the Investigator in this event. The Investigator may also withdraw the Subject from the study at any time based on his/her medical judgment.

If a Subject voluntarily withdraws or is withdrawn from the study for any reason, all end-of-study procedures must be performed. Any adverse events not resolved at the time of withdrawal will be classified as ongoing and the Study Completion/Discontinuation CRF will be completed. The reason for exclusion or withdrawal will be recorded and the appropriate CRFs submitted to the Sponsor.

Subjects must be withdrawn from the study for the following reasons:

- Withdrawal of informed consent (the Subject's decision to withdraw for any reason);
- Any clinical event, laboratory abnormality, or concurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy and participation in the study is not in the best interest of the Subject (Investigator withdrawal);
- Termination of the study by the Sponsor;
- The Subject becomes a prisoner or becomes involuntarily incarcerated for treatment of either a psychiatric or physical illness (e.g., infectious disease)

It is the right and duty of the Investigator to interrupt the treatment of any Subject whose health or well-being maybe threatened by continuation in this study or who may be experiencing unmanageable factors that may interfere with the study procedures or the interpretation of study results. Such Subjects will be withdrawn from the study rather than be allowed to continue under a modified regimen.

5.9. Subject Retention Strategy and Loss to Follow-Up

Subject retention is important to the validity of study outcomes. At the time of subject enrollment and execution of the patient informed consent, the Investigator and/or designee, will discuss the importance of complying with protocol requirements and the follow-up visit schedule (Refer to Section 4.2, Clinical Inclusion Criteria #7). Individual considerations that may preclude a Subject from returning for a study follow-up visit (e.g., transportation, distance, scheduling constraints) should be identified and adequately addressed prior to enrolling a Subject into the study to mitigate future loss to follow-up. At the time of the follow-up visit, the Investigator or designee will again discuss the expectation that the Subject will comply with the protocol's follow-up schedule and address any individual concerns that would prevent continued compliance.

The study objectives may not be realized if a significant number of Subjects are lost to follow-up. A Subject will be considered lost to follow-up and withdrawn from the study once they have missed two consecutive follow-up visits and three documented attempts have been made by the Investigator or designee to contact the Subject or next of kin. One of the three documented attempts must include a certified letter.

5.10. Subject Study Completion

A Subject has completed the study when the 36 month follow-up visit has been completed. Any Subject that does not complete these requirements due to voluntary withdrawal, physician withdrawal, death, or any other reason will be considered a withdrawal. Subjects will not be provided with any medical care by the Sponsor after study completion or withdrawal. Subjects will continue to receive care per institutional standards. All Subjects, regardless of completion or withdrawal, will need a completed Study Completion/Discontinuation CRF.

5.11. Device Deficiencies

The Study Devices are commercially available in the U.S and the EU. Device deficiencies and complaints should be reported through normal product surveillance mechanisms.

5.12. Explant Procedures

The Study Device may be explanted during a surgical procedure or as part of an autopsy. Sites are requested to return explanted device to the Sponsor for gross and histological evaluation. Prior to planned or potential device retrieval, contact the Gore Associate managing the study to communicate that a specimen is being retrieved from a study Subject. A specimen shipping kit will be immediately sent to the Site. The specimen kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

6. Study Administration

6.1. Training

All Investigators implanting devices in this clinical study must be trained on the protocol and Instructions for Use (IFU) by Sponsor associates, designees or another appropriately trained physician at the study Site.

6.2. Monitoring

Site monitoring for this study will be provided by the Sponsor or designee. Monitoring oversight will be provided by the Sponsor.

The Site monitors are qualified by training and experience to oversee the progress of the study at the Site and will ensure that the Investigators and their staff understand and adhere to both the applicable regulatory requirements and the study Protocol. In addition, they may assist in resolution of any problems that may arise during the study.

Site Initiation

Site initiation will be performed to assure that each Investigator and his/her staff understands the Protocol, applicable regulations, human subject protection requirements, and the Investigator's obligations. This visit will ensure that required documentation with the appropriate approval is in place prior to Subject enrollment.

Periodic Site Monitoring

Periodic Site monitoring will occur as necessary to ensure continuing adequacy of facilities and adherence to the study Protocol, the GCPs, and applicable regulations and laws that pertain to the conduct of the study. These activities will also review the CRFs and source documentation, the timely submission of accurate records to the Sponsor, and the maintenance of proper records. A report will be written following each Site visit and a follow up letter will be provided to the Site with a summary of findings. Each Site will also be visited at close-out to ensure all documentation is complete.

6.3. Device Accountability and Storage

The Study Device is commercially available in the U.S. and applicable OUS markets. Each Site will manage devices according to their standard process for commercial devices.

6.4. Core Lab

Core Lab services for this study will be provided by a Sponsor designee for study imaging.

6.5. Protocol Deviations

A Protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. The Investigator is responsible for promptly recording and reporting Protocol Deviations to the Sponsor and the reviewing IRB/EC per IRB/EC policy. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the study and Subject safety and determine if additional reports or actions are required. Additional action may include Site retraining, removal of devices from the Site, and/or Site termination.

The Investigator will not implement any changes to the protocol without first obtaining written agreement from the Sponsor and documented approval from the IRB/EC, except in the event of an immediate hazard(s) to a Subject. The Investigator will report the Protocol Deviation in accordance with the applicable regulations.

6.6. Protocol Amendments
The Investigator will obtain IRB/EC approval on all amendments in a timely manner. The Sponsor will ensure proper training of Investigator and Site staff on all protocol amendments.

6.7. Sponsor Representatives
Sponsor representatives may be present during study procedures to provide technical assistance to the Investigator in the use of the device. The activities of these Sponsor representatives will be supervised by the Investigator.

6.8. Access to Source Data/Documents
Source data are defined as all information necessary for the reconstruction and evaluation of the Clinical Investigation.

The Investigator will keep all study records, source data and investigational devices available for inspection by the Sponsor, Sponsor's monitors, IRB/EC, and regulatory authorities.

6.9. Study Records Retention
The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Records will be maintained during the study and for a minimum of two years after the latter of the date on which the study is terminated or completed, or the date the records are no longer required to support regulatory approval of the device. In any event, study records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but not be limited to:

- All correspondence with another Investigator, an IRB/EC, the Sponsor, a monitor, or Regulatory Authority, including required reports.
- Records of each Subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records, including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
    - Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain the informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
    - All relevant observations, including records concerning adverse device effects (anticipated and unanticipated), the information and date and condition of each Subject upon entering, and information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each Subject to the Study Device, including the date and time of each use, and any other therapy.

- The protocol, any amendments, and documentation of any deviations from the protocol, including the dates and the reasons for such deviations.
- Any other records that Regulatory Authority requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- A certification stating that the IRB/EC is in compliance with Regulatory Authority regulations.
- Any other records as required by the Regulatory Authority, the IRB/EC and the Sponsor.

The Investigator will prepare and submit the following reports:

- Withdrawal of IRB/EC approval: The Investigator will report any withdrawal of approval within 5 working days after the Investigator has been notified of the withdrawal.
- Progress reports: Progress reports documenting the procedure, AEs and follow-up data concerning individual Subjects will be submitted to the Sponsor on standardized CRFs. The Investigator may also be required to submit progress reports and final reports to the IRB/EC and to the Sponsor summarizing the Investigator's experience during the study.
- Protocol Deviations shall be reported as described in Section 6.
- Other: Any other reports as reasonably requested by the Sponsor or required by Regulatory Authority.

6.10. Publication Plan

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. The Sponsor will register the study and post results as required by this policy and applicable U.S. laws and regulations.

7. Data Collection and Submission

The Clinical Data Management System (CDMS) for this study will be provided by:

Medidata Solutions Worldwide
379 Thornall Street, 15th Floor
Edison, New Jersey 08837

7.1. Data Collection Methods

This study will report clinical data using the Medidata Rave® CDMS web-based application. The CDMS will be the database of record for the protocol and subject to regulatory inspections. All users will be trained to use the CDMS and will comply with study specific guidelines/instructions as well as applicable regulatory requirements.

Subject data will be collected using protocol-specific case report forms (CRF). Site staff will enter data directly into the CRF for transmission to the Sponsor. The Sites will be notified of any significant amendments to the CRFs.

7.2. Data Clarification and Correction
Once entered, data will be evaluated to ensure that it is complete, consistent and logically sound. If changes to the data in the CDMS are required, all changes, reasons for changes, and persons making the changes will be captured in the CDMS's audit trail.

7.3. CRF Completion Schedule
Case Report Forms will be completed as soon as reasonably possible during or following each Subject visit.

8. Risk Assessment

8.1. Potential Risks
The risks associated with the GORE® VIABAHN® Endoprosthesis for use in in-stent restenosis are expected to be similar to the risks associated with the use of PTA or other endovascular procedures in the superficial femoral artery.

Such risks associated with these devices, including the GORE® VIABAHN® Endoprosthesis include, but are not limited to:

- Hematoma
- Stenosis
- Thrombosis or occlusion
- Distal embolism
- Side branch occlusion
- Vessel wall trauma and/or rupture
- False aneurysm
- Infection
- Inflammation
- Fever and/or pain in the absence of infection
- Deployment failure
- Malposition
- Malapposition
- Device migration
- Device failure

Risks associated with endovascular procedures include, but are not limited to:

- access site infection
- entry site bleeding and/or hematoma
- vessel thrombosis
- occlusion
- psuedoaneurysm
- trauma to the vessel wall including perforation, rupture, or dissection
- distal embolization
- arteriovenous fistula formation
- transient or permanent contrast induced renal failure
- renal toxicity
- sepsis or shock
- radiation injury

- myocardial infarction
- fever
- pain
- inflammation
- death

The GORE® VIABAHN® Endoprosthesis should not be used in patients with known hypersensitivity to heparin, including those patients who have had a previous incidence of Heparin-Induced Thrombocytopenia (HIT) type II.

8.2. Minimization of Risks

Potential risks associated with the use of the Study Device may be minimized by the following activities:

- The Study Device has been FDA approved for the application being evaluated in this study protocol and for other uses. The Study Device has been CE-marked for the application being evaluated in the study protocol and for other uses.
- The Sponsor has performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production.
- Investigators will be selected who are knowledgeable and experienced in peripheral endovascular procedures.
- Comprehensive Site Investigator and staff training will be conducted to share information regarding design and proper use of the Study Device.
- The Site Investigator, Sub-Investigators, Study Coordinator(s) or designee at each Site will be trained to the protocol and Subject follow-up requirements.
- Protocol inclusion/exclusion criteria and follow-up schedules are designed to select appropriate Subjects and identify potential complications early. Subjects will be assessed post-procedure and subsequently on a regular basis to collect information on the Subject's status and any reportable Adverse Events.
- Data completed by the Sites will be monitored to evaluate protocol compliance and the data for accuracy and Subject safety.
- The Instructions for Use will be provided with the Study Device.

8.3. Summary of Expected Benefits

Subjects may receive no benefit from taking part in this study. The Study Device is expected to improve blood flow in patients with symptomatic peripheral artery disease in the superficial femoral artery.

9. Adverse Events and Safety Monitoring

Adverse Events (AEs) are defined as any untoward medical occurrences in a Subject whether device-related or not.

9.1. Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with PAD patients undergoing endovascular procedure. See Section 8, Risk Assessment.

9.1.1. Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the study device, procedure, or disease. Only one primary relationship will be assigned to each reported AE.

Study Device-related

If functioning or characteristics of the study device caused or contributed significantly to the Adverse Event, the AE would be classified as primarily related to the study device.

Study Procedure-related

If the procedure (and not the device) caused or significantly contributed to the Adverse Event, the AE would be classified as primarily related to the index procedure.

Disease-related

If the Adverse Event was a result of the underlying disease progression for which the study procedure is being performed, and not the device or procedure, the AE would be classified as primarily related to the disease.

Not-related

If an Adverse Event which cannot be attributed to the study device, procedure, or disease, it will be reported as “Not related”.

Unknown relationship

If the relationship of the Adverse Event to the device, procedure, or disease cannot be determined, it will be reported as “Unknown”.

9.1.2. Adverse Event Classification

The severity of each AE will be categorized by the Investigator as either serious or non-serious, as defined below:

Serious Adverse Event (ISO 14155 Definition)

A Serious Adverse Event is an Adverse Event that

- led to death
- led to 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 body function, or
    - inpatient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Non-Serious Adverse Events: generally uncomplicated, resolving without intervention, extension of ongoing medical therapy, or consequence to the Subject.

9.1.3. Adverse Event Reporting and Coding

AEs will be reported on the appropriate case report form (CRF) and documented in the Subject's permanent medical record. The Investigator at each Site is ultimately responsible for reporting AEs to the Sponsor.

The following information on each reported Adverse Event will be collected:

- Adverse Event Name
- Adverse Event Onset Date
- Relationship
- Classification Serious or Non-Serious
- Treatment
- Outcome
- Resolution Date

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The Sponsor is responsible for the MedDRA classification, along with AE reporting and ongoing safety evaluation of the study in accordance with national regulatory requirements

Adverse Event submission guidelines:

- Adverse Event reporting begins once the patient is enrolled in the study following the final assessment of angiographic eligibility requirements during the study procedure. All Adverse Events should be reported from enrollment through study completion/discontinuation.
- Clinical conditions present pre-procedure are not adverse events unless the severity of the condition worsens during the course of the Subject's participation in the study.
- Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. Adverse Events should be reported using the full name without abbreviations or narratives.
- Adverse Events with an outcome status of "Ongoing" should be assessed at each follow-up evaluation to determine if the event has resolved. Adverse Events ongoing at study completion/discontinuation should be left as "Ongoing" on the AE case report form.

9.1.4. Subject Death

Death is not an AE but instead an outcome of an AE. In rare cases the known cause of death or one AE may not be able to be declared as the major contributor to death, however when possible death should be reported as an outcome.

Any ongoing or unresolved AEs at the time of death will be indicated as "ongoing" on the CRF.

Attempts will be made by the Investigative site to obtain death certificates, autopsy reports, and device explants when at all possible.

9.2. Clinical Events Committee

An independent Clinical Event Committee(CEC) will be established to review all safety-related and clinical events during the study. The committee will be composed of three members representing Interventional Radiology, Interventional Cardiology and/or Vascular Surgery.

The scope of the CEC is as follows:

1. General review and adjudication of Adverse Events to include:
    a. Agreement on the Serious Adverse Event designation as coded by Site
    b. Agreement of the relationship of the AE to the study device, index procedure, or disease
    c. Review of MedDRA coding for consistency between similar events
2. Death summary review and agreement of relationship of the death to the study device or index procedure as reported by the Site
3. Protocol Deviation review (as appropriate)
4. General study consultation (as appropriate)

The CEC meetings will be scheduled approximately 3 times per year depending on the rate of enrollment. At minimum, safety data will be reviewed by the committee prior to each 6-month and/or annual due date for a FDA interim report.

10. Statistical Analysis

10.1. Primary Endpoint Analysis

10.1.1. Primary Effectiveness

The primary effectiveness endpoint is Primary Patency at 12 months post-procedure. Primary patency will be estimated through 365 days along with a 95% confidence interval using Kaplan-Meier analysis. Equivalent analysis will be performed with regards to the primary patency partitioning the data by lesion length (< 230 mm and ≥ 230mm). All results will be compared to that obtained in the RELINE study.

10.1.2. Primary Safety

The primary safety endpoint is procedure or device-related Serious Adverse Events within 30 days of the index procedure. The total number of events as well as the number of Subjects experiencing them will be tabulated along with a 95% confidence interval.

10.2. Secondary Endpoint Analysis

10.2.1. Acute Procedural Success

Acute Procedural Success is defined as successful delivery of the study device and complete coverage of the target lesion without a procedure or device-related Serious Adverse Event prior to hospital discharge. This will be tabulated omitting all Subjects with unknown status.

10.2.2. Primary Patency
Primary patency is defined as patent blood flow through the study device, which requires either a PSVR measurement ≤ 2.5 or patent flow indicated by the Core Lab, without repeat intervention. Primary patency will be estimated at 30 days, 12, 24 and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

10.2.3. Primary Assisted Patency
Primary assisted patency is defined as blood flow through the study device regardless of repeat interventions to maintain patency prior to occlusion. Blood flow will require confirmation by the study core lab. Primary assisted patency will be estimated at 30 days, 12, 24 and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

10.2.4. Secondary Patency
Secondary patency is defined as blood flow through the study device regardless of repeat interventions to restore patency after occlusion. Blood flow will require confirmation by the study core lab. Secondary patency will be estimated at 30 days, 12, 24 and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

10.2.5. Freedom from Target Lesion Revascularization (TLR)
Target Lesion Revascularization is defined as a repeat intervention within the study device and 5 mm proximal or distal to the edge of the study device to maintain or re-establish patency. Freedom from TLR will be estimated at 30 days, 12, 24 and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

10.2.6. Freedom from Major Amputation
Major Amputation is defined as removal of the study limb above the metatarsals, resulting from a vascular event. Freedom from major amputation will be estimated at 30 days, 12, 24 and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

10.2.7. Change in Ankle-Brachial Index (ABI)
Ankle Brachial Index is defined as the ankle systolic pressure in the study limb divided by the highest brachial systolic pressure in either arm. The minimum, maximum, median, mean and standard error will be reported for the change in ABI relative to that measured pre-procedure at 30 days, 12, 24 and 36 months. All values measured within the defined window will be used in calculation.

10.2.8. Change in Rutherford Category
The change in Rutherford Category, measured relative to that obtained pre-procedure, will be assessed at 30 days, 12, 24 and 36 months. The minimum, maximum, median, mean and standard error will be reported as well as the counts for each outcome. All values measured within the defined window will be used in calculation.

10.2.9. Stent Fracture
Device stent fractures will be assessed by the study core lab through x-ray images. A table of all stent fractures, which are clearly distinguishable from previously implanted stents, will be reported at 12, 24 and 36 months. All values measured within the defined window will be used in tabulation.

10.3. Additional Analysis

[redacted]

10.4. Sample Size

[redacted]

10.5. Blinding Scheme
Due to the fact that there is only one study treatment, neither the Subjects nor Investigators will be blinded to the study treatment.

10.6. Data Analysis

10.6.1. Timing of Analyses
Reports will be prepared when follow-up is complete for endpoints of the study (e.g. 1-year, 2-year, and 3-year). Additional interim analyses and reports will be done in order to comply with regulatory reporting requirements. This will consist of, at a minimum, the physical characteristics of enrolled Subjects as well as tabulations of all interventions and adverse events. In addition, listings of all interventions and adverse events will be prepared. Once all Subjects have either completed 36 months of follow-up or been withdrawn from the study, a formal statistical analysis will be performed to evaluate all study endpoints.

10.6.2. Analysis Populations
Both of the following populations will be used for analyses of primary and secondary endpoints.
(1) Intent to treat – All patients assigned to the study treatment, regardless of whether or not they received it or have any protocol violations.
(2) Per protocol – A subset of the ITT population consisting of Subjects receiving the study device which meet all inclusion and exclusion criteria and without any major protocol violations.

10.6.3. Pooling of Data
Data from all study sites will be pooled on a clinical basis, i.e., the study sites will follow a common protocol, the study will be monitored to assure compliance with the protocol and applicable government regulations, and the data collection and handling procedures will be the same at all study sites.

11. Ethical and Regulatory Considerations

11.1. Statement of Compliance

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and applicable regulatory requirements.

The following are applicable to this study:

21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 50	Protection of Human Subjects
21 CFR Part 56	Institutional Review Boards
ICH-GCP E6	International Conference on Harmonisation Regulations Guideline For Good Clinical Practice

11.2. Compliance Responsibilities

The Sponsor will conduct the study in accordance with all applicable regulations and laws. The Sponsor will be responsible for documenting that Investigators have the necessary skills, training and information to properly conduct the study. The Sponsor will ensure proper monitoring of the study and ensure the Site has obtained IRB/EC approval prior to enrollment. The Sponsor will provide information to the Investigators, the reviewing IRB/EC and the Food and Drug Administration concerning the progress of and any new material information about the study.

The Investigator will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing IRB/EC and the Food and Drug Administration. The Investigator will ensure IRB/EC approval is obtained prior to enrollment, maintained throughout the course of the study, and that all IRB/EC reporting requirements are met. The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator's care and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is properly obtained.

11.3. Informed Consent

The Investigator shall ensure that all potential Subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.

The formal consent of a Subject, using the IRB/EC-approved consent form, must be obtained by the Investigator before that Subject undergoes any study-related procedure. The consent form will be signed and personally dated by the Subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a Subject's willingness to continue to take part in the study will be provided to the Subject.

The Investigator shall ensure that documentation of the acquisition of informed consent is recorded in each Subject's records in accordance with applicable regulations.

11.4. Independent Ethical Review

The Investigator shall not enroll any Subjects prior to obtaining approval for the study from a properly constituted independent IRB/EC.

The Investigator will submit the protocol, informed consent forms, and other information to be provided to Subjects such as survey instruments or questionnaires, and any proposed advertising/recruitment materials, to the IRB/EC for written approval.

11.5. Conflict of Interest

All Investigators will follow applicable laws and regulations as well as the conflict of interest policies of their Site and the reviewing IRB/EC.

11.6. Confidentiality

All Subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

Such records may also be reviewed by the Site's IRB/EC and other regulatory bodies (e.g., FDA).

The Investigator will inform the Subjects that their records will be reviewed.

11.7. Study Discontinuation or Suspension

If the Sponsor prematurely discontinues the study, all enrolled patients will be followed per the standard of care at each institution. The Sponsor may request that Subjects are telephoned or come in for an office visit prior to study termination.

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