DURABILITY PAS

The US Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal By using the Everflex Nitinol Stent System Post Approval Study

Clinical Investigation Plan Version 3.1
17 November 2016

NCT01680835

Clinical Protocol

**The US StuDy for
EvalUating EndovasculaR TreAtments of Lesions in the
Superficial Femoral Artery and Proximal Popliteal
By usIng the
EverfLex NitInol STent System Post Approval Study**

DURABILITY PAS

Version 3.1

17November2016

CP-1001

**Sponsor: Medtronic
3033 Campus Drive
Suite N550
Plymouth, MN 55441**

Clinical Protocol Acceptance

I have read this clinical protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to 21 CFR Parts 50, 54, 56 and 812, to other applicable regulations, to applicable laws and to hospital Institutional Review Board (IRB) requirements.

_____ _____/_____/_____
Principal Investigator Signature DD MMM YY

_____
Principal Investigator Printed Name

_____
Investigational Site

Protocol Synopsis

The US Stu**D**y for Eval**U**ating Endovascula**R** Tre**A**tments of Lesions in the Superficial Femoral Artery and Proximal Popliteal **B**y us**I**ng the Protégé Everf**L**ex Nit**I**nol S**T**ent S**Y**stem **P**ost **A**pproval **S**tudy (**DURABILITY PAS**)	
Protocol Number	CP-1001
Test Device	EverFlex™ Self-Expanding Peripheral Stent System
Primary Objective	To confirm the long-term safety and effectiveness of the EverFlex™ Self-Expanding Stent System through three years post-procedure.
Study Design	A prospective, multi-center, non-randomized, single arm study to confirm the safety and effectiveness of primary stenting using the EverFlex™ stent compared to a performance goal of PTA in the treatment of atherosclerotic superficial femoral artery (SFA) and proximal popliteal lesions 4-18 cm long in subjects with Rutherford Clinical Categories 2-4.
Follow-Up Schedule	Follow-up assessments will occur at pre-discharge, 30 days, 1 year, 2 years and 3 years.
Number of Subjects	108 subjects will be enrolled
Number of Sites	20 to 30 investigational sites in the United States.
Primary Endpoint	Composite endpoint defined as freedom from acute death, freedom from 36-month amputation, and freedom from 36-month clinically-driven target lesion revascularization compared to a PTA performance goal.
Secondary Endpoints	**1. Freedom from Stent Fracture** Determined by x-ray at 1, 2 and 3 years using the following classifications: Class 0 – No strut fractures Class I – Single tine fracture Class II – Multiple tine fractures Class III – Stent fracture(s) with preserved alignment of the components Class IV – Stent fracture(s) with mal-alignment of the components Class V – Stent fracture(s) in a trans-axial spiral configuration

	AND the following categories: Category A – Restenosis ≤ 50% at site of fracture Category B – Restenosis > 50% at site of fracture Category C – Occlusion at site of fracture Category D – Unable to determine **2. Freedom from acute death, freedom from amputation and freedom from clinically-driven target lesion revascularization at 1 and 2 years** Defined as the absence of all-cause mortality occurring within 30-days, absence of any major amputation within 12-/24- months and the absence of any clinically-driven repeat invasive procedure, including angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter inside or within 10 mm of the previously treated lesion due to the return of clinical symptoms within 12-/24-months of the procedure. **3. Freedom from 36-month amputation** Defined as the absence of any major amputation (removal of the target limb or a part of the target limb above the metatarsal line) within 36 months of the procedure. **4. Freedom from 36-month clinically-driven target lesion revascularization** Defined as the absence of any clinically-driven repeat invasive procedure, including angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter inside or within 10 mm of the previously treated lesion due to the return of clinical symptoms within 36 months of the procedure. **5. Freedom from acute death** Defined as the absence of all-cause mortality occurring within 30 days of the procedure. **6. Device Success** Defined as the ability to deploy the stent as intended at the treatment site. **7. Improvement in Rutherford Clinical Category at 1 Year** Defined as an improvement in clinical status indicated by a decrease of one or more in Rutherford Clinical Category compared to baseline. **8. Improvement in Ankle-Brachial Index at 1 Year** Defined as an increase in the ankle-brachial index (ABI) compared to baseline in subjects with compressible arteries and baseline ABI < 0.9. **9. Walking Improvement at 1 Year** Defined as an increase in Walking Impairment Questionnaire score in

	subjects who did not have iliac disease treated at the time of the index procedure compared to baseline. **10. Adverse Event Rates** Defined as the rate of adverse events that occur during the course of the study; event and subject counts as well as proportions of subjects with events categorized by type will be reported. Note that adverse events are captured at each study assessment. Counts and rates of all-cause mortality will be reported both as part of the overall adverse event profile as above, and separately as a specific outcome.
Timeline	**Date of First IRB Approval:** Q3 2012 **Date of Last IRB Approval:** Q2 2014 **Date of First Subject Enrolled:** 14 January 2013 **Estimated Date of Last Subject Enrolled:** Q1 2015 **Estimated Enrollment Rate:** 0.33 subjects/site/month **Date of 6 Month Report:** 15 August 2012 **Date of 12-Month Report:** 27 February 2013 **Date of 18-Month Report:** 29 August 2013 **Date of 2-Year Report:** 19 February 2014 **Estimated Study Completion Date:** Q4 2018 **Estimated Date of Final Report Submission:** Q4 2018

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

1.0 INTRODUCTION

Purpose

The purpose of this study is to confirm the safety and effectiveness of primary stenting with the EverFlex™ Self-Expanding Peripheral Stent System (EverFlex stent) when used in subjects with atherosclerotic stenoses, restenoses or occlusions of the native superficial femoral artery or superficial femoral and proximal popliteal arteries.

Device Name

EverFlex™ Self-Expanding Peripheral Stent System (EverFlex device) manufactured by ev3.

Indication for use

The EverFlex™ Self-Expanding Peripheral Stent System is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions up to 180 mm in length in native Superficial Femoral Artery (SFA) and/or proximal popliteal arteries with reference vessel diameters ranging from 4.5 – 7.5 mm.

Study Overview

This is a prospective, multi-center, non-randomized, single arm study to confirm the safety and effectiveness of PTA and primary stenting using the EverFlex stent versus a performance goal of PTA alone in the treatment of atherosclerotic superficial femoral artery (SFA) and proximal popliteal lesions 4-18 cm long in subjects with Rutherford Clinical Categories 2-4.

Duration of the Investigation

The estimated duration of the study is approximately five years from the time of first subject enrollment to the last follow-up visit. Subjects will be followed for three years. ev3 plans to submit a final report when all available subjects have completed the 3-year follow-up visit.

Number of Sites and Subjects

One hundred eight (108) subjects will be enrolled at between 20 to 30 investigational sites in the United States. To ensure adequate enrollment, it is expected that participating investigational sites screen all potential subjects for this study.

2.0 DEVICE DESCRIPTION

EverFlex Device Sizes

The EverFlex™ Self-Expanding Stent System is provided in multiple stent lengths (20, 30, 40, 60, 80, 100, 120, 150, and 200 mm) and diameters (6, 7, and 8 mm).

EverFlex Device Components and Principles of Operation

The EverFlex™ Self-Expanding Peripheral Stent System is a self-expanding Nitinol stent system intended for permanent implantation. The self-expanding stent is made of a nickel titanium alloy (Nitinol) and comes pre-mounted on a 6F, 0.035" over-the-wire delivery system. The stent is cut from a Nitinol tube in an open lattice design, and has tantalum radiopaque markers at the proximal and distal ends of the stent. Upon deployment, the stent achieves its predetermined diameter and exerts a constant, gentle outward force to establish patency.

For specific information on device components and steps on how to operate the EverFlex device, refer to the *Instructions for Use*.

3.0 BACKGROUND AND SIGNIFICANCE

Disease Overview

Atherosclerosis is a thickening, hardening and loss of elasticity of the walls of arteries characterized by the focal accumulation of lipids, fibrous tissue and calcium deposits in the arteries. Atherosclerotic disease within the superficial femoral and proximal popliteal arteries can lead to flow-limiting stenoses or occlusions that are observed clinically as intermittent claudication, asymptomatic functional impairment or critical limb ischemia.[1] A primary therapeutic goal among patients with atherosclerotic disease is the maintenance of patency in the superficial femoral and proximal popliteal arteries. Treatment by percutaneous angioplasty with or without stenting of stenotic and occluded lesions within the SFA has demonstrated success in treating short, focal lesions, but limited success in maintaining long-term patency in longer lesions.[2-15]

Summary of Clinical Trials in the SFA with the EverFlex Stent

DURABILITY I

DURABILITY I (Study Measuring the Durability of the Protégé® EverFlex™ Stent in Lesions of the Superficial Femoral Artery), was a multi-center, non-randomized, prospective study. It was designed to evaluate the safety and efficacy of the EverFlex stent in the treatment of *de novo*, restenotic or reoccluded SFA lesions in symptomatic PAD patients. Bosiers et al. published a report on DURABILITY I Study one-year outcomes.[16] The study enrolled 151 subjects (151 target lesions) between August, 2006 and June, 2007 at 13 centers is Europe. A total of 161 stents (158 EverFlex) were implanted: single stents in 93.4% (141/151) and a second stent in 6.6% (10/151). The primary endpoint of the study, the

primary patency rate determined by duplex ultrasound, defined as a target vessel with less than 50% diameter stenosis at 12 months and no reintervention of the target vessel, was 72.2%. Freedom from restenosis data was available for 99.3% (133/134) of the subject who completed a 12-month follow-up visit. The mean Rutherford classification fell from 2.8±0.8 (range 1-5) at baseline to 0.6±1.1 (range 0-5) at 12 months. The mean ankle-brachial index rose from 0.6±0.2 (range 0-1.4) at baseline to 0.9±0.2 (range 0-1.2) at 12 months. The rates for freedom from >50% restenosis at 6 and 12 months were 91.3% (95% CI 84.92 to 95.2%) and 72.2% (95% CI 63.8% to 79.6%), respectively. The freedom from the target lesion revascularization rate at 12 months was 79.1% (95% CI 71.2 to 85.6%). The 1-year stent fracture rate was 8.1% (95% CI 4.0 to 14.4%). Elongation of the PROTÉGÉ EverFlex stent during implantation was identified in 90% (9/10) of the fractured stents at 12 months. The author concluded that the high freedom from >50% restenosis and low fracture rate at 12 months suggested that the PROTÉGÉ EverFlex stent offered a safe and acceptably efficacious means of treating SFA lesions in symptomatic subjects with PAD.

DURABILITY II

ev3 conducted a study titled "The US Study for Evaluating Endovascular Treatment of Lesions in the Superficial Femoral Artery and Proximal Popliteal by using the Protégé EverFlex Nitinol Stent System II (DURABILITY II). DURABILITY II was a prospective, multi-center, non-randomized, single arm study to evaluate the safety and effectiveness of primary stenting with a single EverFlex stent compared to PTA performance goals for the treatment of stenotic, restenotic or occluded lesions (non-stented) of the native superficial femoral artery or the superficial femoral and proximal popliteal arteries.

The primary safety endpoint of the study was major adverse event rate at 30-days, defined as clinically-driven target lesion revascularization, amputation of treated limb, or all-cause mortality. The primary effectiveness endpoint, stent patency (defined as PSVR <2.0 at the stented targeted lesion with no clinically-driven reintervention) rate at 12 months was determined by duplex ultrasound. Subjects were followed yearly for 3 years with duplex ultrasound to determine stent patency, radiograms of the stented extremity to assess stent fractures and ankle brachial indices. Clinical assessment of change in Rutherford Category was planned for 1-year post intervention.

DURABILITY II enrolled 287 subjects at 44 investigational sites in both the United States and Europe. A total of 303 stents were implanted: single stents in 95% (272/287), and 5.0% (15/287) received multiple stents. The mean age of subjects was 68 years, with 66% male. Co-morbidities include hypertension (88%), hyperlipidemia (86%), and diabetes (43%). The mean lesion length measured by core laboratory was 89.1 mm. The mean normal-to-normal lesion length measured by sites was 109.6 mm. Deployment of the stent at the intended treatment site was achieved in 99.3% of subjects. No major adverse events occurred at 30 days. Primary duplex ultrasound stent patency at 1 year in all subjects including single-stent and multi-stent implants was 67.7%. The primary patency by Kaplan Meier estimate at 1 year was 77.2%. At 2 and 3 years, primary patency was 66.1% and 60.0%, respectively. The mean Rutherford classification fell from 2.8±0.6 (range 2-5) at baseline to 0.6±1.1 (range 0-5) at 1 year. The mean ankle-brachial index rose from 0.65 ± 0.15 (range 0.06-0.89) at baseline to 0.89 ± 0.20 (range 0.25-1.77), 0.88 ± 0.19 (range 0.26, 1.27) and 0.89 ± 0.19

(range 0.31, 1.33) at 1, 2, and 3 years, respectively. The 1-year stent fracture rate was 0.4%; and was 0.9% at 2 and 3 years, respectively.

DURABILITY 200

DURABILITY 200 was an investigator–sponsored, prospective, nonrandomized study performed at two centers in Belgium designed to evaluate primary stenting with the Protégé EverFlex 200 mm long self-expanding nitinol stent in femoropopliteal TransAtlantic Inter-Society Consensus (TASC) C and D lesions of at least 150 mm in length.[17] The primary study endpoint, primary patency at 12 months, defined as the absence of hemodynamically significant stenosis on duplex ultrasound imaging (systolic velocity ratio <2.4) at the target lesion and without target lesion revascularization (TLR) <12 months. Stent fracture occurrence was assessed at the 12–month follow-up by conventional x-ray imaging. Between March 2008 and June 2009, 100 patients with symptomatic TASC C and D femoropopliteal lesions were treated with at least one 200-mm-long EverFlex stent. A total of 158 EverFlex stents were implanted: one stent in 49% (49/100), two stents in 44% (44/100) and three stents in7% (7/100) of patients. The average lesion length was 242 mm (range, 160-450mm). The primary patency rate by Kaplan-Meir estimate at 12 months was 64.8%. The 12-month freedom from target lesion revascularization by Kaplan-Meier estimate was 68.2%. Stent fractures were identified in 6 of 100 patients, resulting in a 12-month stent fracture rate of 6%.

Clinical Experience with the EverFlex Stent

Ruef et al.[18] were the first to report clinical experience with the EverFlex stent in the SFA. A total of 12 subjects were treated for total occlusions (n=9) or long stenoses (n=3) in the SFA, with a mean lesion length of 14.9 cm. One subject had a thrombus detected prior to pre-dilatation that was resolved by treatment with Abciximab (ReoPro®). Subjects returned for follow-up visits 6-8 weeks after the procedure. All subjects were free of claudication in the treated leg, ankle-brachial indices revealed a 100% patency rate in all treated legs, and duplex ultrasound confirmed 100% stent patency (no definition provided) at 6-8 weeks post-implant. These results demonstrate good short-term clinical results for stenting in the SFA using the EverFlex stent.

4.0 METHODOLOGY

Study Design

DURABILITY PAS is a prospective, multi-center, non-randomized, single arm study with sequential enrollment of all qualified subjects undergoing treatment of atherosclerotic lesions in the native superficial femoral artery or the superficial femoral and proximal popliteal arteries. All eligible subjects who provide informed consent will undergo PTA and stenting using the EverFlex device. Follow-up will take place at pre-discharge, 30 days, 1 year, 2 years and 3 years.

Study Objective and Primary Endpoints

The objective of the study is to confirm the safety and effectiveness of primary stenting using the EverFlex device compared to a percutaneous transluminal Angioplasty (PTA) performance goal for the treatment of stenotic, restenotic or occluded lesions (non-stented) of the native superficial femoral artery or the superficial femoral and proximal popliteal arteries.

Primary Endpoint

The primary endpoint of the study is composite endpoint defined as freedom from acute death, freedom from 36-month amputation, and freedom from 36-month clinically-driven target lesion revascularization compared to a PTA performance goal.

Secondary Endpoints

The secondary endpoints are:

1. ***Freedom from Stent Fracture:*** Determined by x-ray at 1, 2 and 3 years using the following classifications:
   Class 0 – No strut fractures
   Class I – Single tine fracture
   Class II – Multiple tine fractures
   Class III – Stent fracture(s) with preserved alignment of the components
   Class IV – Stent fracture(s) with mal-alignment of the components
   Class V – Stent fracture(s) in a trans-axial spiral configuration

   AND the following categories:
   Category A – Restenosis ≤ 50% at site of fracture
   Category B – Restenosis > 50% at site of fracture
   Category C – Occlusion at site of fracture
   Category D – Unable to determine

2. ***Freedom from acute death, freedom from amputation and freedom from clinically-driven target lesion revascularization at 1 and 2 years:*** Defined as the absence of all-cause mortality occurring within 30-days, absence of any major amputation within 12-/24- months and the absence of any clinically-driven repeat invasive procedure, including angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter inside or within 10 mm of the previously treated lesion due to the return of clinical symptoms within 12-/24-months of the procedure.
3. ***Freedom from 36-month amputation:*** Defined as the absence of any major amputation (removal of the target limb or a part of the target limb above the metatarsal line) within 36 months of the procedure.
4. ***Freedom from 36-month clinically-driven target lesion revascularization:*** Defined as the absence of any clinically-driven repeat invasive procedure, including

angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter inside or within 10 mm of the previously treated lesion due to the return of clinical symptoms within 36 months of the procedure.

5. ***Freedom from acute death:*** Defined as the absence of all-cause mortality occurring within 30-days of the procedure.
6. ***Device Success:*** Defined as the ability to deploy the stent as intended at the treatment site.
7. ***Improvement in Rutherford Clinical Category at 1 Year:*** Defined as an improvement in clinical status indicated by a decrease of one or more in Rutherford Clinical Category compared to baseline.
8. ***Improvement in Ankle-Brachial Index at 1 Year:*** Defined as an increase in the ankle-brachial index (ABI) compared to baseline in subjects with compressible arteries and baseline ABI < 0.9.
9. ***Walking Improvement at 1 Year:*** Defined as an increase in Walking Impairment Questionnaire score in subjects who did not have iliac disease treated at the time of the index procedure compared to baseline.
10. ***Adverse Event Rate:*** Defined as the rate of adverse events that occur during the course of the study; event and subject counts as well as proportions of subjects with events categorized by type will be reported. Note that adverse events are captured at each study assessment. Counts and rates of all-cause mortality will be reported both as part of the overall adverse event profile as above, and separately as a specific outcome.

Subject Selection Criteria

Assessment is performed based on data available to the investigator at the time of enrollment.

General Inclusion Criteria

Subjects must meet all of the following general inclusion criteria.

1. Has stenotic, restenotic (from PTA or adjunct therapy, not including stents or stent grafts), or occluded lesion(s) located in the native superficial femoral artery or superficial femoral and proximal popliteal arteries suitable for primary stenting.
2. Has a Rutherford Clinical Category Score of 2, 3 or 4.
3. Is willing to comply with all follow-up evaluations at the specified times.
4. Is ≥ 18 years old.
5. Provides written informed consent prior to enrollment in the study.

Angiographic Inclusion Criteria

Subjects must meet all of the following angiographic inclusion criteria. The implanting physician bases all angiographic inclusion criteria on visual determination at the time of the procedure.

1. Target lesion(s) located within the native SFA/proximal popliteal: distal point at least 3 cm above the cortical margin of the femur and proximal point at least 1 cm below the origin of the *profunda femoralis* measured by straight posteroanterior (PA) view for distal lesions, ipsilateral oblique view for proximal lesions. Refer to *Figure 1* for a diagram of a PA view of the distal femur and identification of the cortical margin.
2. Evidence of ≥ 50% stenosis or restenosis (from PTA or adjunct therapy, not including stents or stent grafts), or occlusion of target lesion(s).
3. Target lesion(s) total length is ≥ 4 cm and ≤ 18 cm.
4. Target vessel diameter is ≥ 4.5 mm and ≤ 7.5 mm.
5. There is evidence of at least one runoff vessel to the ankle/foot of the limb to be treated that does not also require treatment for significant (> 50% stenosis or occlusion) stenosis during the index procedure.

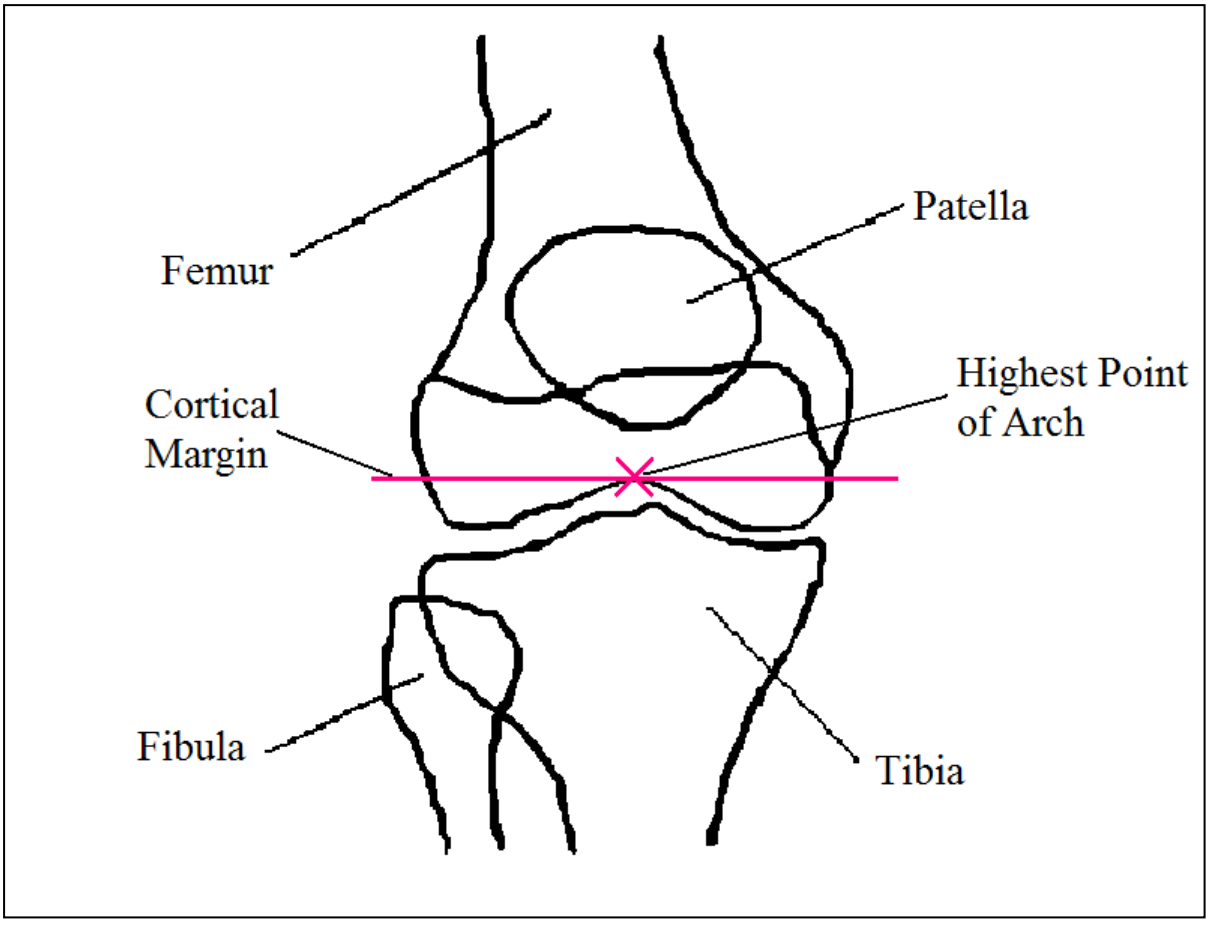


Figure 1: PA View of Distal Femur and Definition of Cortical Margin

The line defining the cortical margin is perpendicular to the femur and includes the highest point in the cortical arch. No part of the lesion should be closer than 3 cm from the line defining the cortical margin.

General Exclusion Criteria

The subject must not meet any of the following general exclusion criteria.

1. Has undergone previous implantation of stent(s) or stent graft(s) in the target vessel.
2. Has a contraindication or known allergy to antiplatelet therapy, anticoagulants, thrombolytic drugs, contrast media or any other drug used in study according to the protocol.
3. Has known hypersensitivity to nickel-titanium.
4. Has bleeding diathesis, coagulopathy, known hypercoagulable condition, or refuses blood transfusion.
5. Female currently breastfeeding, pregnant, or of childbearing potential not using adequate contraceptive measures.
6. Has life expectancy of less than 1 year.
7. Has planned use of thrombectomy, atherectomy, brachytherapy or laser devices during procedure.
8. Has previously been enrolled in the DURABILITY PAS study.
9. Has received endovascular treatment of target lesion by percutaneous transluminal angioplasty or any other means of previous endovascular treatment (e.g. cutting balloon, scoring balloon, cryoplasty, thrombectomy, atherectomy, brachytherapy or laser devices) within six months of the index procedure.
10. Has any planned surgical intervention or endovascular procedure 14 days before or 30 days after the index procedure.
11. Is currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
12. Has any co-morbid condition that precludes endovascular treatment.

Angiographic Exclusion Criteria

The subject must not meet any of the following angiographic exclusion criteria. The implanting physician bases all angiographic exclusion criteria on visual determination at the time of the procedure.

1. Exchangeable guidewire cannot cross the target lesion and/or re-enter true vessel lumen distal to lesion(s).
2. Presence of significant (> 50% stenosis or occlusion) ipsilateral common femoral stenosis.
3. Aneurysmal target vessel.
4. Presence of an acute intraluminal thrombus at the proposed lesion site.
5. Perforation, dissection or other injury of the access or target vessel requiring additional stenting or surgical intervention prior to start of PTA procedure.

6. Focal popliteal disease in the absence of femoral disease.

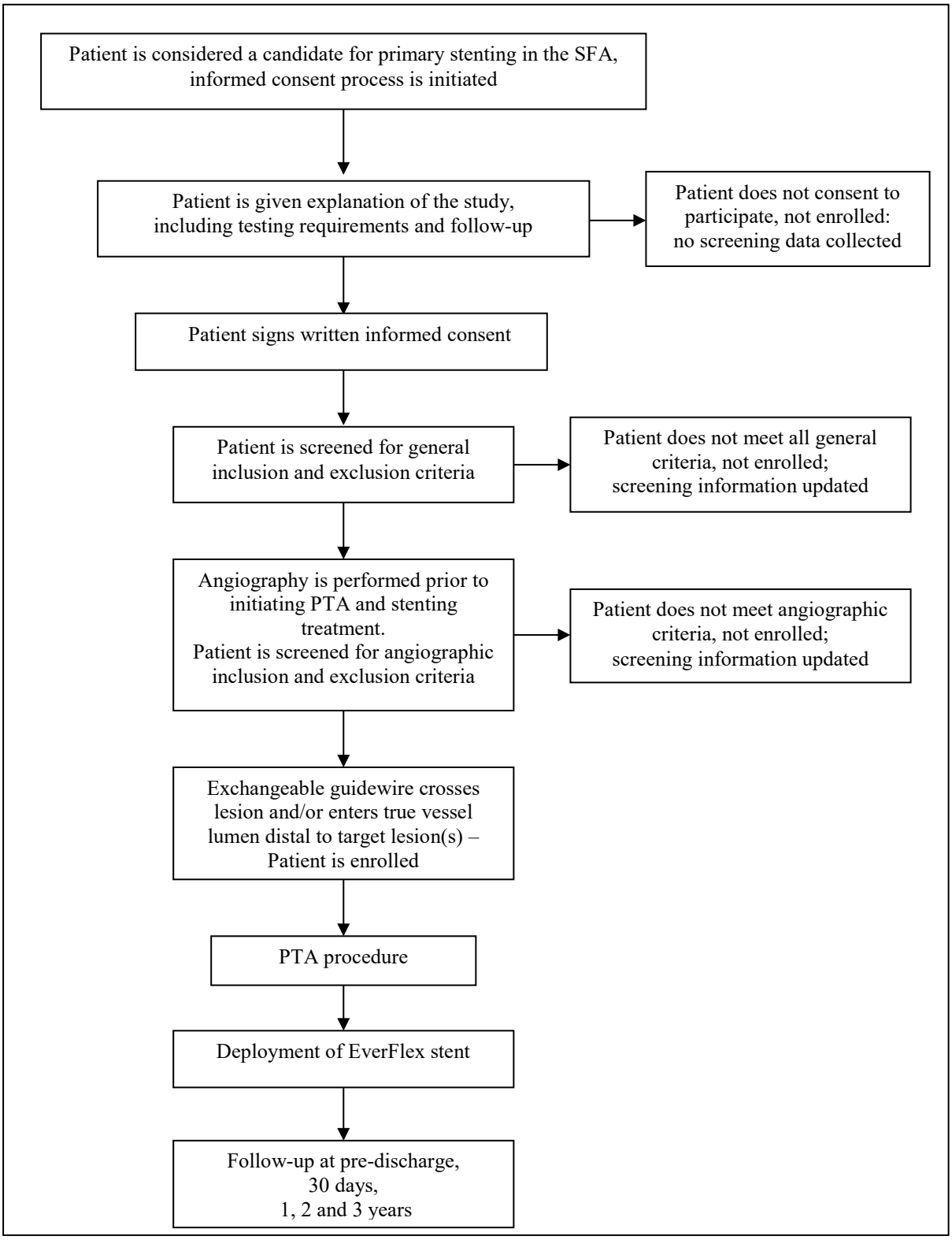
Patient Screening

It is expected that all potentially eligible patients be approached for enrollment in the study and be screened at the investigational site. Eligible patients will be given an explanation of the study, educated on the possible risks and benefits to participating, and be asked to provide written informed consent prior to any study-specific screening or testing. Patients will be informed that, despite signing the informed consent document, screening procedures may demonstrate that the patient is not a suitable candidate for the study.

Subject Enrollment

The subject is enrolled in the study after he/she has signed the subject informed consent and it has been determined that he/she meets all of the inclusion criteria and none of the exclusion criteria. The point of enrollment is defined as the moment an exchangeable guidewire crosses the lesion and/or re-enters the true vessel lumen distal to the target lesion(s). *Figure 2* provides a flow diagram from the point of subject screening through continuing follow-up visits.

Figure 2: Study Flow Diagram from Subject Screening to Follow-up



Overview of Study Conduct

Table 1 provides an overview of the assessment requirements for the study, and Tables 2-7 provide the specific requirements at each stage of the study.

Table 1: Study Assessment Requirements

Assessment Schedule (Timeframe Window)	Baseline (45 days prior, labs 30 days prior)	Procedure	Pre-Discharge	30 Days (25-40 Days)	1 Year (335-395 Days)	2 Years (685-775 Days)	3 Years (1050-1140 Days)
Medical history	X						
Physical exam	X						
Clinical status by Rutherford Clinical Category	X			X	X		
Ankle-brachial index†	X			X	X	X	X
Walking Impairment Questionnaire	X			X	X	X	X
Angiogram†		X					
Laboratory tests‡	X						
X-ray (fracture assessment) †					X	X	X
Adverse event documentation		X	X	X	X	X	X
Amputation		X	X	X	X	X	X
Death		X	X	X	X	X	X
Clinically Driven Target Lesion Revascularization		X	X	X	X	X	X

†If a subject requires a re-intervention of the target vessel, a resting ABI, x-ray evaluation for stent fracture and angiogram are to be performed prior to the procedure. If possible, all non-invasive assessments should be captured for the study, including ABI, and x-ray evaluation, even if the re-intervention and angiogram are declined.

‡Creatinine and White Blood Cell count

Performance of study assessments at unscheduled follow-up visits should be done as clinically indicated and corresponding data must be submitted to the sponsor.

Baseline Requirements

Baseline data collection requirements are identified in Table 2. Baseline assessment results will be submitted to the sponsor.

Table 2: Baseline Requirements

Baseline Requirements	Timeframe Window
Medical history	Within 45 days
Physical exam	
Clinical status by Rutherford Clinical Category	
Ankle-brachial index	
Walking Impairment Questionnaire	
Laboratory tests (creatinine and white blood cell count)	Within 30 days

Procedure Requirements

The subject will undergo percutaneous revascularization of the SFA, which may include the proximal popliteal artery using the EverFlex device in conjunction with any FDA approved angioplasty balloon.

The following describes the required assessments and activities during the procedure.

Angiogram

A sheath will be inserted and after insertion the subject should be anticoagulated according to the discretion of the implanting physician. Selective angiography of the leg to be treated including the distal aorta, bilateral iliac, ipsilateral femoral, popliteal and tibial vessels (to the level of the ankle) will be performed to identify the anatomical characteristics of the vasculature and to best isolate and define the lesion. The distal-most point of the lesion should be at least 3 cm above the plane defining the cortical margin of the femur measured by straight posteroanterior (PA) view. (Refer to *Figure 1* for a diagram of a PA view of the distal femur, identifying the cortical margin.) Angiography must be conducted according the angiographic core lab protocol (see Manual of Operations).

During angiography the implanting physician will assess the subject for the angiographic inclusion and exclusion criteria. This includes verifying that the target lesion(s) total length is ≥ 4 cm and ≤ 18 cm. If the subject meets all the angiographic inclusion criteria and does not meet any of the angiographic exclusion criteria, the subject is enrolled when an exchangeable guidewire crosses the lesion and/or re-enters the true vessel lumen distal to the target lesion(s).

Angiograms will be obtained immediately prior to and after the angioplasty and stenting procedure to document pre- and post-treatment results. Copies of all angiograms must be sent to the angiographic core lab.

The angiographic core lab values will supersede the implanting physician's measurement assessments for data analysis purposes; however, the implanting physician's assessment will be used to determine subject eligibility at the time of enrollment.

Angioplasty and Stenting

Standard PTA techniques will be followed for balloon dilatation prior to stent deployment and documented. Use of any devices other than PTA balloons, cutting balloons, and scoring balloons for recanalization (e.g. thrombectomy, atherectomy, brachytherapy or laser devices) during the index procedure will be considered a deviation of the clinical protocol. The use of PTA balloons, guidewires, and devices to facilitate placement of a guidewire distal to the target lesion, (e.g. Covidien Viance™, Covidien Enteer™, Cordis Frontrunner® CTO Re-Entry Catheter, and the Cordis Outback® LTD™ Re-Entry Catheter) during the index procedure will not be considered a deviation of the clinical protocol.

If the subject requires treatment of an atherosclerotic lesion in the iliac artery, this will be ALLOWED during the index procedure, either prior to or after the treatment of the SFA lesion. If the iliac artery treatment is completed prior to the SFA treatment, iliac artery treatment success (< 30% residual stenosis with no perforation, dissection or other injury requiring additional stenting or surgical intervention) must occur prior to the point of enrollment. If the iliac artery treatment is completed after the SFA treatment, < 30% iliac artery residual stenosis must be accomplished and verification of patency in the stented SFA segment must be completed via angiography. Documentation of the results for the iliac procedure either prior to or after the SFA treatment will be recorded.

The selection of the EverFlex stent size, deployment and withdrawal of the delivery system will follow the procedures described in the *Instructions for Use* provided in the Manual of Operations. Only one EverFlex stent should be used to treat the target lesion(s). The treatment of diffuse lesions is only allowed under the condition that the entire target area can be covered using a single stent. The distal-most point of the stent should be at least 3 cm above the line defining the cortical margin of the femur measured by straight posteroanterior (PA) view. The line defining the cortical margin is perpendicular to the femur and includes the highest point in the cortical arch.

While the intent of the study is to confirm the safety and effectiveness of primary stenting using a single EverFlex stent, should the implanting physician deem it necessary for the safety of the subject to implant a second stent over the target lesion, the second implant must also be an EverFlex stent. The selection of the additional stent size, deployment and withdrawal of the delivery system will follow the procedures described in the *Instructions for Use* provided in the Manual of Operations.

Standard PTA techniques will be followed for balloon dilatation after stent deployment. Using fluoroscopy, the stent should be visualized to verify full deployment. If stent

expansion is incomplete at any point along the lesion, post deployment balloon dilation via standard PTA technique should be performed. Note that the EverFlex stent cannot be expanded past its predetermined diameter.

Interventions below the knee will only be allowed for restoration of patency that was compromised as a result of the index procedure.

Any adverse events that occur during the procedure must be documented.

The end of the procedure is defined as the time the last guidewire and catheter have been removed **AND** a complete angiogram, including runoff, has been performed post-treatment. If the subject returns to the procedure room and a guiding catheter is reinserted and dilation is performed, this is considered a re-intervention and should be documented accordingly. The sheath(s) may be removed at the implanting physician's discretion.

Angiographic screening and procedure requirements are specified in Table 3.

Table 3: Angiographic Screening and Procedure Requirements

Angiographic Screening and Procedure Requirements
1. Selective angiography of the distal aorta, bilateral iliac, ipsilateral femoral, popliteal and tibial vessels (to the level of the ankle), films to document pre-treatment vasculature (per core lab protocol).
2. Verification that the subject meets all angiographic inclusion criteria and none of the angiographic exclusion criteria.
3. Verification that the target lesion(s) total length is ≥ 4 cm and ≤ 18 cm.
4. Verify an exchangeable guidewire has crossed the lesion and/or re-entered the true vessel lumen distal to the target lesion(s).
5. Subject enrollment.
6. Balloon angioplasty pre-dilatation using standard PTA techniques prior to stent placement.
7. EverFlex stent deployment and delivery system withdrawal according to *Instructions for Use.*
8. Post-deployment dilatation using standard PTA techniques, if incomplete stent expansion exists.
9. Selective angiography, including runoff, of the vessel to document final results (per core lab protocol).
10. Guidewire and catheter are removed, end of procedure.
11. Record device use assessment.
12. Adverse event documentation, including any procedural complications.
13. Primary Endpoint Assessments: Amputation, Death, Clinically Driven Target Lesion Revascularization

Medical Anticoagulant/Antiplatelet Therapy

Subjects should receive anticoagulation and antiplatelet therapy according to the implanting physician's standard of care. The medical regiment must be recorded on the subjects case report form.

Follow-Up Requirements

Pre-Discharge Requirements

All subjects will be assessed pre-discharge. At this time, an evaluation for adverse events (AEs) will be completed and documented. Pre-discharge assessment requirements are listed in Table 4.

Table 4: Pre-Discharge Assessment Requirements

Pre-Discharge Requirements	Timeframe
Adverse event documentation	Prior to discharge
Primary Endpoint Assessments: Amputation, Death, Clinically Driven Target Lesion Revascularization	

30-Day Follow-up Requirements

All subjects are required to have a follow-up visit at 30 days. At this time, clinical staging by Rutherford Clinical Category, ankle-brachial index, Walking Impairment Questionnaire, and an evaluation for AEs will be completed and documented. Table 5 lists the 30-day follow-up assessment requirements.

Table 5: 30-Day Follow-Up Assessment Requirements

30-Day Follow-up Requirements	Follow-up Window
Clinical status by Rutherford Clinical Category	25-40 Days Post-Procedure
Ankle-brachial index	
Walking Impairment Questionnaire	
Adverse event documentation	
Primary Endpoint Assessments: Amputation, Death, Clinically Driven Target Lesion Revascularization	

1-Year Follow-Up Requirements

All subjects are required to have a follow-up visit at 1 year. Clinical staging by Rutherford Clinical Category, ankle-brachial index, Walking Impairment Questionnaire, and an evaluation for AEs will be completed and documented. X-ray imaging to identify stent fracture is also required. Refer to the Manual of Operations for the x-ray imaging and transmission requirements.

X-rays should be sent out to the core laboratory for evaluation within five business days. The core laboratory will review the x-rays for quality and the presence of stent fracture. The core laboratory will communicate to the investigational site within seven business days after receiving the x-rays if the image quality is inadequate to make an assessment of stent fracture and will also provide guidance on specific measures for the site to take in order to adequately assess for stent fracture. If the image quality of the x-ray is inadequate to make an assessment of stent fracture, the investigational site must request that the subject return for a second series of x-rays.

Study coordinators will be trained on the quality assessment measures used for x-ray acquisition for stent fracture assessment. It is recommended that the study coordinators be present at the time of the x-ray acquisition to provide direction and guidance to the x-ray personnel. Each site must review x-rays for image quality prior to sending to core lab.

Table 6 lists the 1-year follow-up assessment requirements.

Table 6: 1-Year Follow-up Assessment Requirements

1-Year Follow-up Requirements	Follow-up Window
Clinical status by Rutherford Clinical Category	1-Year Visit: 335-395 Days Post-Procedure
Ankle-brachial index	
Walking Impairment Questionnaire	
X-ray	
Adverse event documentation	
Primary Endpoint Assessments: Amputation, Death, Clinically Driven Target Lesion Revascularization	

2-Year and 3-Year Follow-Up Requirements

All subjects are required to have follow-up visits at 2 and 3 years. Ankle-brachial index Walking Impairment Questionnaire, and an evaluation for AEs will be completed and documented at each visit. X-ray imaging to identify stent fracture is also required. Refer to the Manual of Operations for the x-ray imaging and transmission requirements.

X-rays should be sent out to the core laboratory for evaluation within five business days. The core laboratory will review the x-rays for quality and the presence of stent fracture. The core laboratory will communicate to the investigational site within seven business days after receiving the x-rays if the image quality is inadequate to make an assessment of stent fracture and will also provide guidance on specific measures for the site to take in order to adequately assess for stent fracture. If the image quality of the x-ray is inadequate to make an assessment of stent fracture, the investigational site must request that the subject return for a second series of x-rays.

Study coordinators will be trained on the quality assessment measures used for x-ray acquisition for stent fracture assessment. It is recommended that the study coordinators be

present at the time of the x-ray acquisition to provide direction and guidance to the x-ray personnel. Each site must review x-rays for image quality prior to sending to core lab.

Table 7 lists the 2-year and 3-year follow-up assessment requirements.

Table 7: 2-Year and 3-Year Follow-up Assessment Requirements

2-Year and 3-Year Follow-up Requirements	Follow-up Window
Ankle-brachial index	2-Year Visit: 685-775 Days Post-Procedure 3-Year Visit: 1050-1140 Days Post-Procedure
Walking Impairment Questionnaire	
X-ray	
Adverse event documentation	
Primary Endpoint Assessments: Amputation, Death, Clinically Driven Target Lesion Revascularization	

All-cause mortality at 1, 2 and 3 years will be reported.

Unscheduled Assessments During Follow-up

Performance of study assessments at other follow up visits should be done as clinically indicated and corresponding data must be documented and submitted to the sponsor.

If a subject is clinically indicated for a re-intervention of the target vessel, a resting ABI, x-ray evaluation for stent fracture and angiogram are to be performed and documented prior to the endovascular procedure. If possible, all non-invasive assessments should be captured for the study, including ABI, and x-ray evaluation, even if the re-intervention and angiogram are declined. If the subject does not want to undergo an angiogram, re-intervention, or non-invasive assessments it will not be considered a deviation from the clinical protocol. In the event a subject declines to proceed with an angiogram,re-intervention, or non-invasive testing, the reason will be documented in the subject's medical record.

Termination of Participation

All subjects have the right to terminate themselves from participation at any point during the study. In addition, Principal Investigators also have the ability to terminate subject participation in the study (see page 26, "Subject Withdrawal" for rationale for physician-directed withdrawal). A description of the reason for their termination will be documented. Reasons for termination include: completion of study, subject withdrawal, physician-directed subject withdrawal, lost-to-follow-up, and death.

Loss to Follow-Up

Every attempt must be made to have all subjects complete the follow up visit schedule. A subject will not be considered lost-to-follow-up unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone and if contact via phone is not successful, then a certified letter from the Principal Investigator must be sent to the subject's last known address. Both telephone and letter contact efforts to obtain follow up must be documented in both the subject's medical records and on the study case report forms (CRFs).

Subject Withdrawal

All study subjects have the right to withdraw their consent at any time during the study. Whenever possible, the site staff should obtain written documentation from the subject that wishes to withdraw his/her consent for future follow-up visits and contact. If the site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate CRFs must be completed for the subject and clear documentation of the subject's withdrawal be provided to the sponsor.

Withdrawal of a subject from the study can occur at the direction of the Principal Investigator or the sponsor. Acceptable reasons for physician-directed subject withdrawal are; the subject is not adhering to the protocol requirements, the subject has enrolled in another study that conflicts with the DURABILITY PAS primary endpoint, or if the physician deems it in the best interest for the safety or welfare of the subject to withdraw.

Deviations to the Investigation

Principal Investigators and site staffs must avoid all protocol deviations. Use of any devices other than PTA balloons for recanalization (e.g. cutting balloon, scoring balloon, thrombectomy, atherectomy, brachytherapy or laser devices) during the index procedure will be considered a deviation of the clinical protocol. Use of embolic protection devices during the index procedure will also be considered a deviation of the clinical protocol. Only the use of PTA balloons, guidewires, and devices to facilitate placement of a guidewire distal to the target lesion (e.g. Cordis Frontrunner® CTO Re-Entry Catheter, the Cordis Outback® LTD™ Re-Entry Catheter, and the Kensey Nash Safe-Cross® System) during the index procedure will not be considered a deviation of the clinical protocol. The sponsor will not make any exceptions to the protocol and will not provide waivers to subjects with any protocol deviations. Any emergency deviations (deviations from the protocol to protect the life or physical well being of a subject; e.g. use of a device not approved for use in the superficial femoral artery) that occur must be reported to the sponsor and the site IRB per their guidelines.

While this clinical protocol is designed to study the safety and effectiveness of the EverFlex device in subjects who received only one stent, the sponsor recognizes there may be circumstances necessitating the need to implant more than one stent in the superficial femoral artery during the index procedure. Implantation of a second stent in the SFA during the

index procedure is not considered a protocol deviation. The sponsor will track and report all instances when more than one stent is implanted in the SFA during the index procedure, including information on the reason(s) why the additional stent was needed, as well as the investigator and site.

Device Malfunctions

A device malfunction occurs in any case when the device does not perform in its intended function when used in accordance with the *Instructions for Use*. All device malfunctions must be reported to the sponsor.

If a device malfunction results in an adverse event for the subject, this adverse event will be considered a reportable adverse event and must be reported as an adverse event. Device malfunctions that do not result in an adverse event for the subject do not need to be recorded as an AE, as they are not considered an AE.

If a device malfunction occurs with the EverFlex device, return the device to ev3, following the procedure outlined in the Regulatory Binder.

Adverse Events

The following adverse events, as defined below, will be reported in this study.

Procedural Adverse Events (AEs) are defined as any event, regardless of severity, that occurs during the index procedure through the pre-discharge visit. The sponsor should be notified in a timely manner. If the Procedural AE is determined to be an SAE, follow reporting guidelines for SAEs below.

Major Adverse Events (MAEs) are defined as: clinically-driven target lesion revascularization, amputation of treated limb, and all-cause mortality. All MAEs should be reported as soon as possible after the investigational site's knowledge of the event. A written report will be provided to the sponsor within 10 business days after the investigator learns of an MAE and must be provided to the IRB according to the board's reporting guidelines.

Serious Adverse Events (SAEs) are any adverse events that result in death, are life threatening, require inpatient hospitalization greater than 24 hours, or prolongation of an existing hospitalization, require intervention to prevent permanent impairment/damage, or result in persistent or significant disability/incapacity. A written report will be provided to the sponsor within 10 business days after the investigator learns of an SAE and must be provided to the IRB according to the board's reporting guidelines.

An **Unanticipated Adverse Device Effect (UADE)** is defined as any serious adverse experience (event) leading to injury, illness, or death of a subject not previously identified in nature, severity or degree of incidence in the protocol that may be directly related to the use of the device.

In the event of a UADE the investigational site will inform the sponsor and IRB as soon as possible. A written report will be provided to the sponsor within 10 business days after the investigator learns an unanticipated adverse device effect and will be provided to the IRB according to the board's reporting guidelines.

Deaths

Each subject death must be reported to the sponsor. A death must be reported to the sponsor as soon as possible after the site's knowledge of the event. A written report will be provided to the sponsor within 10 business days after the investigator learns of a death and will be provided to the IRB according to the board's reporting guidelines. It is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the sponsor when available. Any other source documents related to the death should also be provided to the sponsor. In the event that no source documents are available the PI will be required to submit a letter to the sponsor describing the circumstances of the subject's death.

Core Laboratory Requirements

Angiographic Core Laboratory

An independent Angiographic Core Laboratory will review all scheduled and unscheduled angiographic procedure data. See Angiographic Core Laboratory Procedures in the Manual of Operations.

The Angiographic Core Laboratory is:

Jeffrey J. Popma, MD
Medical Director
Beth Israel Deaconess Medical Center Angiographic Core Laboratory
940-W Commonwealth Ave, 2nd Floor
Boston, MA 02215
Phone: 617-307-5520
Fax: 617-307-5612

X-ray Core Laboratory

An independent x-ray Core Laboratory will review all scheduled and unscheduled x-ray data. See X-ray Core Laboratory Procedures in the Manual of Operations.

The X-ray Core Laboratory is:

Jeffrey J. Popma, MD
Medical Director
Beth Israel Deaconess Medical Center Angiographic Core Laboratory
940-W Commonwealth Ave, 2nd Floor
Boston, MA 02215
Phone: 617-307-5520
Fax: 617-307-5612

X-rays should be sent out to the core laboratory for evaluation within two to five business days. The core laboratory will review the x-rays for quality and the presence of stent fracture using the "Stent Location and Integrity Grid". The core laboratory will communicate to the investigational site within seven business days after receiving the x-rays if the image quality is inadequate to make an assessment of stent fracture and will also provide guidance on specific measures for the site to take in order to adequately assess for stent fracture. If the image quality of the x-ray is inadequate to make an assessment of stent fracture, the investigational site must request that the subject return for a second series of x-rays.

There will be a Stent Fracture Adjudication Committee formed to adjudicate the classification and categorization of stent fractures. Clinical summaries describing baseline demographic information, physical findings, medical history and clinical symptomatology will be prepared for the Stent Fracture Adjudication Committee.

Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established. The CEC will consist of physicians who are not investigators in the study and who do not have any significant investment in ev3 or any of their entities. The committee will include, but not be limited to, the specialties of interventional cardiology, vascular surgery, and interventional radiology.

The CEC is responsible for conducting a review of all adverse events, including SAEs and MAEs, reported for study subjects in the study. The CEC will adjudicate and classify all primary and secondary endpoint events as defined in the clinical protocol. In addition, the CEC will be responsible for adjudicating and classifying any site reported device-related, procedure-related or study requirement-related adverse events. The CEC will determine if any device-related adverse event is an unanticipated adverse device effect.

Case Report Forms

Electronic case report forms (eCRFs) will be used to collect study data. The eCRFs will be electronically viewed and signed by the Principal Investigator. All appropriate sections of the eCRFs must be completed.

Case report forms related to the index procedure should be completed within two weeks following subject discharge. The follow-up forms must be completed in a timely manner after the follow-up visit.

Study monitors designated by the sponsor will review the information documented in the eCRFs and verify the information recorded is consistent with medical records and other source documents. Errors or incomplete entries will be rectified.

The sponsor will use the study data for statistical and tracking purposes and will treat the information as confidential. A representative of the FDA may review or copy study records during an audit.

5.0 STATISTICAL METHODS

Primary Endpoint and Sample Size Adjustment

Hypothesis Testing

The study's primary endpoint has been previously defined. The associated statistical hypothesis is that the resulting event-free rate at 36 months is greater than the Performance Goal (PG), which is adapted from RESILIENT 3-year data on freedom from TLR for PTA subjects.

The null and alternative hypotheses for the primary endpoint are:

H_0: $\pi_t \leq \pi_{pg}$

Ha: $\pi_t > \pi_{pg}$

where π_t is the event-free rate in subjects treated with an EverFlex device and π_{pg} is the PG of 35%.

Analysis of this endpoint will be carried out by Kaplan-Meier methods. The point estimate of the event-free rate at 36 months (1095 days) from the date of the index procedure will be computed along with its one-sided 97.5% lower confidence bound. If the lower bound is greater than 35%, it will be declared that the PG and the corresponding primary study objective have been met.

Justification of Performance Goal

The structure of the composite endpoint is derived from a 12-month composite endpoint described by VIVA Physicians Inc. (VPI) as part of their development of safety and effectiveness Performance Goals (PG) for the use of bare nitinol stents in the treatment of femoropopliteal lesions.[19, 20] The VPI 12-month composite was defined as acute death, index limb amputation and target vessel revascularization (TVR) through 12-months. This composite event rate in the studies reviewed was 30.5% at 12 months (Table 8). However, there were no long-term follow-up to 3 years reported.

Table 8: PTA Performance Goals – Safety Data

	Company A (n=29)	Company B (n=24)	Company C (n=63)	Combined (n=116)
12 month Composite (acute death, 12m TVR, 12m amputation	38.5% (10/26)	33.3% (6/18)	25.5% (13/51)	**30.5% (20/95)**

Recently, 3-year data on freedom from TLR was presented on the PTA arm of the RESILIENT study.[21] The reported event-free rate at 3 years among RESILIENT subjects randomized to PTA treatment was 41.8%, a value which is adjusted as follows to account for longer lesions enrolled in DURABILITY II.

The statistical model employed is a Cox regression on the outcome of freedom from TLR applied to DURABILITY II data. Lesion length (in mm) as measured by the core laboratory was the predictor of outcome, resulting in a point estimate of 0.01543 for the logarithm of the hazard ratio, and therefore a hazard ratio of $e^{0.01543}$=1.0155 per mm of lesion length (with longer lesions associated with lower freedom-from-TLR rates).

As the mean lesion length in RESILIENT was 68 mm versus 89 mm in DURABILITY II, the resulting adjusted event-free rate can be obtained using a formula analogous to adjusting with odds ratios:

$$\pi_{pg}/(1-\pi_{pg}) = (0.418/(1-0.418))*1.0155^{(89-68)}$$

Solving this equation gives π_{pg} = 0.342, which is rounded up to give the PG of 35%. Note that this PG is conservative in that it (1) does not attempt to account for any other systematic differences between RESILIENT and DURABILITY II and (2) does not explicitly account for the other elements of the composite endpoint (since these were not presented for RESILIENT), which if included would lower the expected freedom-from-event rate below that seen for TLR alone.

Potential Outcomes

Table 9 summarizes approximate outcomes under potential results for freedom from event, using binomial estimation. Note that the actual analysis will be conducted using time-to-event methods and is subject to currently unknown censoring times, and that therefore the actual success criteria will vary slightly from those noted below.

Table 9: Approximation to Possible Outcomes and Corresponding 97.5% Lower Confidence Bound

Primary Endpoint (PG=35%)			
Sample Size	**Count of subjects with freedom from event**	**36-Month Freedom From Event Rate**	**97.5% lower confidence bound**
108	**48**	**44.4%**	**35.1%**
108	49	45.4%	36.0%
108	50	46.3%	36.9%
108	51	47.2%	37.8%

Sample Size and Power

The required sample size for evaluating the primary endpoint can be approximated using the normal method for testing a single proportion (as above, under Kaplan-Meier methods the actual power will vary slightly from this calculation):

$$n = \frac{(\pi_{pg} \times (1-\pi_{pg})) \times (Z_{1-\alpha} + Z_{1-\beta}\sqrt{\pi_t(1-\pi_t)/(\pi_{pg}(1-\pi_{pg}))})^2}{(\pi_t - \pi_{pg})^2}$$

Where,

- Type I error (α) = 0.025 (one-sided)
- Statistical power ($1 - \beta$) = 90%
- Z is the standard normal deviate for α =0.025 and β=0.10.
- π_t is estimated freedom-from-event at 36 months
- π_{pg} is the PG

Using this approximation with $\pi_t = 0.55$ (estimated from current DURABILITY II data), $\pi_{pg} = 0.35$ (the *a priori* performance goal), $Z_{1-\alpha} = 1.96$ and $Z_{1-\beta} = 1.28$ gives a sample size of 62. Allowing for approximately 30% of subjects lacking a 3-year follow-up visit, the needed sample size under this approximation for 90% power is a minimum of 89.

An additional sample size requirement is based on the secondary endpoint of freedom from stent fracture at 1 year. In DURABILITY I and DURABILITY II, 1-year stent fracture rates of 8.1% (n=151) and 0.4% (n=287), respectively, were observed. The pooled fracture rate of these two studies is 3.0% (13/438), around which a confidence interval of specified width is desired. The desired precision is 7.2% (half-width of 3.6%); we therefore find a 95% two-sided normal confidence interval with upper bound 3.0% + 3.6% = 6.6%, and extract the relevant sample size.

Table 10: Sample Size Freedom from Stent Fracture

Sample Size for Freedom from Stent Fracture			
Sample Size	**Count of subjects with event**	**Event Rate**	**97.5% upper confidence bound (95% two-sided)**
95	3	3.16%	6.67%
96	3	3.13%	6.61%
97	**3**	**3.09%**	**6.54%**
98	3	3.06%	6.47%

From the above table, the required sample size at 1 year is 97 subjects. Considering a 10% rate of attrition, a minimum of 108 subjects are needed, which is larger than the sample size

of 89 calculated for the primary endpoint. The enrolled sample size is therefore 108. Please note that multiple stents are allowed in each subject in the study. The stent fracture endpoint will be analyzed on stent level. To be conservative, sample size calculation is performed on subject level. Therefore more stents than the above assumption may be included in the analysis.

Data Analysis Plan

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.2 or above, SAS Institute Inc. Cary, N.C.) or other widely accepted statistical or graphical software. In general, data for all study subjects combined will be presented. Individual data will be presented in subject listings.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross-tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

For adverse event reporting, the primary analysis will be based on subject counts, not event counts. A subject with more than one event will be counted only once toward the event rate based on the total number of subjects with adverse events.

Unless otherwise specified, statistical significance will be declared when $p<0.05$ for two-sided tests and $p<0.025$ for one-sided tests such as the primary endpoint.

Analysis of Secondary Endpoints

For secondary endpoints, descriptive statistics will be provided. No formal statistical hypothesis testing will be performed. Categorical variables will be analyzed using frequency tabulation and event rate. For continuous variables, analysis will include mean, median, standard deviation, and ranges. Time-to-event variables including the primary endpoint and the secondary endpoint of freedom from stent fracture will be analyzed using survival analysis and reported at 1 year (365 days), 2 years (730 days) and 3 years (1095 days), with Kaplan-Meier plots provided.

Analysis of Ability to Pool Data Across Investigational Sites

This is a multi-center clinical study, with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison across all sites will be completed to determine if the generated data could be pooled. The following variables will be completed to assess the appropriateness of pooling data from across all sites:

- Baseline demographics such as age and gender
- Lesion characteristics such as lesion length and percent stenosis

The distributions of the above variables across the sites will be tabulated. To detect site differences, t-tests or Wilcoxon's rank-sum test will be used for continuous variables and Fisher's exact test for categorical variables.

6.0 RISK/BENEFIT ANALYSIS

The study is designed to minimize risk through observance of strict site and investigator selection criteria, careful subject selection and management, and rigorous adherence to a standardized schedule of post-procedure evaluations.

Potential Benefits

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the EverFlex stent may improve blood flow through the treated artery. This may result in subjects experiencing fewer or less severe leg symptoms.

Information gained from the conduct of this study may be of benefit to other persons with the same medical condition.

Potential Risks

Risks Associated with Peripheral PTA and Stenting

The risks associated with PTA and stenting of the SFA, including the proximal popliteal artery may include but are not limited to the following.

Table 11: Risks Associated with Peripheral PTA and Stenting

POTENTIAL ADVERSE EVENTS The potential adverse effects (e.g., complications) that may occur and/or require intervention with the use of this device include, but are not limited to:	
• Abrupt or sub-acute closure • Allergic reaction to device materials or procedure medications • Allergic reaction to Nitinol • Amputation • Aneurysm • Angina • Arrhythmia • Arterio-venous fistula • Artery perforation or rupture • Bleeding requiring transfusion • Bruising • Contrast medium reaction/renal failure • Death • Device breakage • Dissection or intimal flap • Edema • Embolism • Failure to deploy stent • Fever • Gastrointestinal bleeding due to anticoagulation • Hematoma • Hypertension/hypotension •	• Infection • Inflammation • Intraluminal thrombus • Myocardial infarction • Pain • Partial stent deployment • Pseudoaneurysm • Renal failure requiring dialysis • Renal insufficiency (new or worsening) • Restenosis • Sepsis • Shock • Stent collapse or fracture • Stent migration • Stent misplacement • Stroke • Surgical or endovascular intervention • Thrombosis/occlusion of the stent • Transient ischemic attack • Venous thromboembolism • Vessel spasm

As with any device requiring mechanical deployment and retraction, such as the EverFlex device, there exists a risk of mechanical failure of the device resulting in potential surgical intervention to remove the stent or delivery system.

It is expected that the fluoroscopy time of the stenting procedure will be minimally longer (in order to confirm angiographic inclusion and exclusion criteria) than the time required for stenting procedures using other devices and will not pose additional risks to the subject or laboratory personnel.

All of the above could cause prolonged illness, permanent impairment of daily function, or, in rare cases, death. Possible treatments could include, but are not limited to cardiac surgery and vascular surgery.

Extensive reliability engineering testing has been performed on the EverFlex device to mitigate risks to the subject due to product failure. Additionally, studies using the EverFlex device have been conducted to ensure that the system performs as intended without introducing more risks during the index procedure or during follow-up. Risks of the EverFlex stent may be further limited by providing medications such as aspirin or clopidogrel and continuing to monitor subjects following stent implantation.

While some of the potential risks identified have occurred in prior stent implantation studies, and while ev3 believes that the risk for significant injury or death due to the EverFlex device is quite low, these risks have yet to be adequately and fully quantified. Eligibility criteria that exclude subjects who are at higher risk for experiencing an anticipated adverse event have been selected in order to reduce the potential risks to subjects that participate in this study.

Risks Associated with Required Medications

There are also anticipated risks associated with recommended medications.

Subjects should receive anticoagulation and antiplatelet therapy according to the implanting physician's standard of care.

It is recommended that subjects receive aspirin indefinitely for atherosclerotic therapy. The standard risks associated with long-term aspirin therapy as described in the product labeling apply. These risks may include gastrointestinal symptoms such as nausea, vomiting, stomach pain and gastrointestinal bleeding. Other complications such as ringing in the ears, liver toxicity, rash, kidney impairment, vertigo and lightheadedness can also occur.

Subjects also should receive clopidogrel for at least four weeks following their EverFlex stent implantation. The standard risks associated with short-term use of clopidogrel as described in the product labeling apply. The risks of clopidogrel may include chest pain, flu-like symptoms, pain, headache, dizziness, upset stomach, bruising and respiratory infection. The major risk of taking a combination of aspirin and clopidogrel for any period of time is possible increase in the risk of a bleeding event.

Risks Associated with Magnetic Resonance Imaging

The use of Magnetic Resonance Imaging (MRI) can induce electrical voltages and currents on the implanted stent, causing heating around the device that may potentially result in tissue damage. Non-clinical testing demonstrates that the EverFlex stent is MR Conditional.

Refer to the *Instructions for Use* for additional safety information on MRI use.

7.0 SITE REQUIREMENTS

Site Selection

The sponsor or a representative of the sponsor will assess each potential site to ensure the Principal Investigator and his/her staff has the facilities and expertise required for the study.

Principal Investigators and sites will be selected based upon the following factors:

- Previous experience with clinical research and percutaneous procedures, including substantial experience treating the superficial femoral artery in the past 12 months
- Currently treating subjects who meet the inclusion/exclusion criteria
- Ability to enroll an adequate number of subjects
- Ability to perform required clinical testing, including: fluoroscopy and x-ray.
- Ability and willingness to provide the sponsor's representatives access to the hospital records, study files, and subject files as they pertain to the study
- Willingness to participate, including compliance with all aspects of the study
- Adequate staffing to conduct the study. This includes:

Principal Investigator	Responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs CRFs indicating documents are accurate and complete.
Sub-Investigator(s)	Responsible for study activities in coordination with Principal Investigator and in accordance to the investigational plan. A site is not required to have a sub-investigator.
Study Coordinator	Assists Principal Investigator with study activities as delegated by the Principal Investigator, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing and providing CRFs to the sponsor in a timely manner.

Training/Initiation Visit

The sponsor or a representative of the sponsor will conduct a training session with each Investigator and his/her staff to review the protocol, *Instructions for Use* of the EverFlex device, CRFs, the informed consent process, IRB involvement and guidelines, responsibilities and obligations, reporting requirements and general guidelines for good clinical practices.

Prior to enrolling subjects at an investigational site, the following documentation must be provided to the sponsor:

IRB approval for the Clinical Protocol

IRB approval for the Principal Investigator to conduct the study

IRB and sponsor approved Informed Consent Form for the study

Investigator(s') *curriculum vitae* (CV)

Laboratory Certification

Financial Disclosure(s) for the Principal Investigator and sub-investigators

Signed Investigator Agreement and if applicable, Sub-Investigator Agreement(s)

Training Log documenting each implanting physician has been trained on the EverFlex device.

Training Log documentation to verify the appropriate study staff has been trained in on the protocol, device, CRFs and study conduct.

8.0 MONITORING PROCEDURES

Monitoring Procedures

ev3 as the sponsor will be responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted. Appropriately trained personnel appointed by ev3 will conduct monitoring at each site. Monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, investigational device accountability, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed investigator agreement, and compliance with IRB conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the Principal Investigator/site staff is cause for the sponsor to put the investigator/site staff on probation or withdraw the investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

Monitoring Reports

After each monitoring visit, the monitor will send to the Principal Investigator a letter summarizing the monitoring visit. A monitoring report will be sent to the sponsor. The report will include the date of the monitoring visit, the site name, the name of the monitor, the name of the investigator, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. The Principal Investigator will be responsible for ensuring that follow-up actions needed to resolve issues at the site are completed in an accurate and timely manner.

Final Monitoring Visit

Final monitoring visits at the sites will be conducted at the close of the study. The purpose of the final visit is to collect all outstanding study data documents, ensure that the Principal Investigator's files are accurate and complete, review record retention requirements with the Principal Investigator, make a final accounting of all study supplies shipped to the Principal Investigator/site, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

9.0 RESPONSIBILITIES, RECORDS and REPORTS

Responsibilities and Record Retention

The Principal Investigator/site must maintain adequate records on all aspects of the study, including the following:

- IRB approvals
- Device disposition
- Informed Consent Forms
- Case Report Forms
- Adverse Event Form and information
- Protocol Deviations
- Correspondence file regarding study
- Subject termination information

The Principal Investigator/site must maintain the study records for at least two years after cessation of the study, or the date that the records are no longer required for purposes of supporting a PMA or notice of completion of a product development protocol, and must contact the sponsor prior to disposal of study records. Records custody may be transferred to another person who will accept responsibility for them. Notice of transfer should be provided in writing by the principal investigator to the sponsor and follow reporting requirements of 21CRF812.

Reports

Reports that are the Principal Investigator's responsibility to generate are listed in Table 11. The table also displays information regarding to whom this information is to be sent, and the frequency and time constraints around report submission. If applicable laws, regulations, or IRB requirements mandate stricter reporting requirements then those listed, the stricter requirements must be followed.

Table 12: Principal Investigator Reporting Responsibilities

Type of Report	Principal Investigator Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Adverse Events	Sponsor	At the time of procedure.
Major Adverse Events	Sponsor and IRB	ASAP, but to Sponsor no later than 10 working days after Principal Investigator is first aware of the event. To IRB according to their guidelines.

Type of Report	Principal Investigator Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Serious Adverse Events	Sponsor and IRB	ASAP, but to Sponsor no later than 10 working days after Principal Investigator is first aware of the event. To IRB according to board guidelines.
Unanticipated Adverse Device Effects	Sponsor and IRB	Written -ASAP, but to sponsor no later than 10 working days after investigators are first aware of the effect. To IRB according to board guidelines.
Withdrawal of IRB Approval or other action on part of the IRB that affects the study	Sponsor	Written – Within 5 working days of IRB decision.
Progress Reports	IRB	At intervals dictated by the IRB, but no less than yearly.
Emergency Deviations from Protocol	Sponsor and IRB	ASAP but to sponsor no later than 5 working days after the deviation occurs. To IRB according to board guidelines.
Inappropriate Informed Consent	Sponsor and IRB	To sponsor within 5 working days after the deviation occurs. To IRB according to board guidelines.
Final Report	Sponsor and IRB	To sponsor within 3 months after termination or completion of study or investigator's participation. To IRB according to board guidelines.
Other	IRB, FDA	Upon request, provide accurate, complete, and current information about any aspect of the study

10.0 DEFINITIONS

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

Adverse Event Definitions

Procedural Adverse Event (AE)	Any adverse event, regardless of severity, that occurs during the index procedure through the pre-discharge visit.
Major Adverse Event (MAE)	A primary safety endpoint adverse event. MAEs are defined as: clinically-driven target lesion revascularization, amputation of treated limb, and all-cause mortality.
Serious Adverse Event (SAE)	Any adverse event that results in death, is life threatening, requires inpatient hospitalization greater than 24 hours, or prolongation of an existing hospitalization, requires intervention to prevent permanent impairment/damage, or results in persistent or significant disability/incapacity.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse experience (event) leading to injury, illness, or death of a subject not previously identified in nature, severity or degree of incidence in the study protocol, literature, or application (including a supplementary plan or application) that may be directly related to the use of the device.

Allergic Reaction: Allergic reaction which could result in nausea, rash, wheezing, edema, induced thrombotic events, urticaria or shock.

Amputation: Surgical removal of the target limb or a part of the target limb above the metatarsal line that was unanticipated prior to the index procedure.

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

Ankle-Brachial Index (ABI): The ratio of the highest ankle systolic pressure to the highest brachial systolic pressure as determined by Doppler ultrasound.

Artery Perforation: Extravasation of contrast media outside the arterial adventitial space.

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

As-Treated Analysis: An "as-treated" analysis is one in which all the participants in a study are analyzed according to the treatment received, regardless of the initial assignment and regardless of the amount of follow-up.

Arterio-venous Fistula: A communication between an artery and a vein in which the arterial blood flows directly into a neighboring vein.

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

Compressible Artery[1]: An artery without significant calcification that can be evaluated by duplex ultrasound; an artery that results in an ABI value < 1.3.

Contrast Medium Reaction: A reaction to the contrast media used in endovascular procedures. Reactions include but are not limited to urticaria, nausea, vomiting, headache and renal failure.

Death: The termination of life.

Device Malfunction: Defined as a malfunction of the EverFlex stent or a component of the delivery system such that it did not perform its intended function when used in accordance with the *Instructions for Use*.

Device-Relatedness Categories for Adverse Events:

> **Device-Related Adverse Event:** AE that has a strong temporal relationship to the presence or performance of the investigational device/system and an alternative etiology is highly unlikely.
>
> **Probably Device-Related Adverse Event:** AE has a strong temporal relationship to the presence or performance of the investigational device/system and an alternative etiology is less likely compared to the potential relationship to the investigational device/system.
>
> **Probably Not Device-Related Adverse Event:** AE had minimal or no temporal relationship to the use of the investigational device/system and/or a more likely alternative etiology exists.
>
> **Not Device-Related Adverse Event:** AE is due to the underlying disease state or concomitant medication or therapy, and was not caused by the investigational device/system.

Device Success: The ability to deploy the stent as intended at the treatment site.

Diabetes (History of): Defined as subjects who have been diagnosed with either Type I or Type II diabetes and are currently taking oral hypoglycemics or insulin.

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

Discharge: The time point when the subject is released from the admitting hospital, transferred to another facility, or has expired.

Dissection: Intimal disruption of vessel the wall with or without medial or adventitial contrast staining. See also **National Heart, Lung and Blood Institute (NHLBI) Classification of Dissection.**

Distal Embolization: Migration of air, plaque, thrombus, or debris that occludes the distal target vessel or one of its branches.

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

Emergent Surgical Revascularization: Surgery performed on an urgent or emergent basis as a result of the PTA procedure and/or use of the EverFlex device.

Enrollment: The subject is enrolled in the study after he/she has signed the patient informed consent and has been determined to meet all inclusion and none of the exclusion criteria. The point of enrollment is defined as the moment an exchangeable guidewire crosses the lesion and/or enters the true vessel lumen distal to the target lesion(s).

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

Focal Popliteal Disease: Entire lesion is located distal to adductor canal on AP view.

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

Hemorrhage: Bleeding requiring hospitalization, repeat procedure, operation or transfusion.

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

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

Index Procedure: The procedure in which the subject has the EverFlex stent implanted or an implant is attempted.

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

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

Intimal Flap: Superficial dissection of the vessel that does not result in medial or adventitial contrast staining (NIHLBI Type A dissection).

Intention-to-treat (ITT) Analysis: An intention-to-treat analysis is one in which data from all participants in a study are analyzed according to the allocated treatment, regardless of the treatment actually received.

Intraluminal Thrombus: A blood clot within a vessel.

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

Myocardial Infarction (MI): Per the ESC/ACC definition[2]:

Criteria for acute, evolving or recent MI.

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) ischemic symptoms;
   b) development of pathologic Q waves on the ECG;
   c) ECG changes indicative of ischemia (ST segment elevation or depression); or coronary artery intervention (e.g., coronary angioplasty).
   d) Pathologic findings of an acute MI.

Criteria for established MI.

Any one of the following criteria satisfies the diagnosis for established MI:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathologic findings of a healed or healing MI.

[2] Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000 Sep;36(3):959-69.

National Heart, Lung and Blood Institute (NHLBI) Classification of Dissection[3]:

Dissection	Description
Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of 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 delayed runoff of the contrast material in the distal vessel
Type E	Persistent luminal filling defect with delayed runoff of the contrast material in the distal vessel
Type F	Filling defect accompanied by total coronary occlusion

New York Heart Association (NYHA) Heart Failure Classification[4]:

Class	Description
Class I:	Subject has no physical limitation and is asymptomatic
Class II:	Subject has mild symptoms while doing light exercise or activities of daily living
Class III:	Subject has difficulty doing simple activities of daily living
Class IV:	Subject is frequently bed- or chair-ridden for most of the day and is too weak and short of breath to do simple activities

Occlusion: 100% stenosis within an artery.

Percent Stenosis: Native vessel diameter as measured at the most narrow point of the lesion divided by the estimated native vessel diameter (the mean of the vessel diameters proximal and distal to the lesion) at that location.

$$\% \text{ Stenosis} = \frac{Diameter\ at\ most\ narrow\ point\ of\ lesion\ (mm)}{\left[\left(proximal\ vessel\ diameter + distal\ vessel\ diameter\right)/2\right]}$$

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

[3] Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol 1991; 68: 467-71.
[4] The Criteria Committee of the New York Heart Association: Physical capacity with heart disease, in Diseases of the Heart and Blood Vessels, Nomenclature and Criteria for Diagnosis, ed 6. Boston, Little, Brown & Co, 1964, pp 110-114

Pre-Procedure: The time until the PTA and stenting procedure begins (before the femoral artery access is obtained).

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

Procedure-Relatedness Categories for Adverse Event:

> **Procedure-Related Adverse Event:** AE that has a strong temporal relationship to the implantation procedure and an alternative etiology is highly unlikely.
>
> **Probably Procedure-Related Adverse Event:** AE has a strong temporal relationship to the implantation procedure and an alternative etiology is less likely compared to the potential relationship to the implantation procedure.
>
> **Probably Not Procedure-Related Adverse Event:** AE had minimal or no temporal relationship to the implantation procedure and/or a more likely alternative etiology exists.
>
> **Not Procedure-Related Adverse Event:** AE is due to the underlying disease state or concomitant medication or therapy, and was not caused by the implantation procedure.

Protocol Deviation: Any divergence from the study protocol (investigational plan); this does not include implantation of a second stent.

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

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

Renal Insufficiency: A 30% increase in serum creatinine from baseline.

Restenosis: The recurrence of abnormal narrowing of an artery after treatment.

Runoff Vessel: An artery distal to treated vessel, including the popliteal, anterior tibial and posterior tibial arteries.

Rutherford Clinical Category[5]: A classification system of clinical categories of chronic limb ischemia ranging from 0 to 6.

The categories, clinical descriptions and objective criteria are:

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

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

*Categories 4, 5, and 6 are embraced by the term chronic *critical* ischemia.

Sepsis: Systemic inflammatory response to infection.

Shock: A condition in which the cells of the body receive inadequate amounts of oxygen secondary to changes in perfusion; most commonly secondary to blood loss or sepsis.

Stenosis: An abnormal narrowing of an artery.

Stent Fracture: Determined by x-ray at 1, 2 and 3 years using the following classifications:

Class 0 – No strut fractures
Class I – Single tine fracture
Class II – Multiple tine fractures
Class III – Stent fracture(s) with preserved alignment of the components
Class IV – Stent fracture(s) with mal-alignment of the components
Class V – Stent fracture(s) in a trans-axial spiral configuration

AND the following categories:
Category A – Restenosis < 50% at site of fracture
Category B – Restenosis > 50% at site of fracture
Category C – Occlusion at site of fracture
Category D – Unable to determine

Stent Migration: Substantial movement of the EverFlex stent from the initial deployment position, noted during the index procedure or via follow-up imaging. This does not include mis-measurement of the lesion, foreshortening or mis-sizing of the vessel.

Stent Misplacement: A stent that is not deployed at the target location.

Stroke: A neurological deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing infarction[6].

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

Sub-acute Closure: Vessel occlusion at the site of treatment between 24 hours and 4 weeks after successful index procedure.

Sub-Investigator(s): Physician(s) responsible for study activities in coordination with Principal Investigator and in accordance to the investigational plan. A site is not required to have a sub-investigator.

Target Lesion Revascularization: Any repeat invasive procedure, including angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter inside or within 10 mm of the previously treated lesion.

> **Clinically-Driven Target Lesion Revascularizations** are those in which the patient has a ≥ 50% diameter stenosis in the presence of recurrent symptoms or a ≥ 70% stenosis without any symptoms (i.e. decreased ABI, symptomatic claudication, etc) in the treated segment.
>
> **Non-Clinically-Driven Target Lesion Revascularizations** are those in which the patient undergoes a non-emergent revascularization for a diameter stenosis < 70% in the absence of recurrent claudication, a positive functional study (if available), or worsened ABI.

Target Vessel Revascularization: Any re-treatment by an invasive procedure, including angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter of the target vessel.

> **Clinically-Driven Target Vessel Revascularizations** are those in which the patient has a ≥ 50% diameter stenosis in the presence of recurrent symptoms or a ≥ 70% stenosis without any symptoms (i.e. decreased ABI, symptomatic claudication, etc) in the treated vessel.
>
> **Non-Clinically-Driven Target Vessel Revascularizations** are those in which the patient undergoes a non-emergent revascularization for a diameter stenosis < 70% in the absence of recurrent claudication, a positive functional study (if available), or worsened ABI.

Thrombosis: The formation or development of a blood clot.

[6] Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack--proposal for a new definition. *N Engl J Med.* Nov 21 2002;347(21):1713-1716.

Transient Ischemic Attack (TIA): A neurological deficit lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction.[6]

Unanticipated Adverse Device Effect: Any serious adverse experience (event) leading to injury, illness, or death of a subject not previously identified in nature, severity or degree of incidence in the protocol, literature, or application (including a supplementary plan or application) that may be directly related to the use of the device.

Vessel Spasm: A sudden, brief tightening of a blood vessel.

Walking Impairment Questionnaire (WIQ): A self-reported quality of life assessment focused on difficulty in walking. Refer to the Manual of Operations for a copy of the WIQ.

Appendix A: Contacts

Sponsor:
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Appendix B: References

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* Mar 21 2006;113(11):e463-654.

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12. van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. *Eur J Vasc Endovasc Surg.* Aug 2004;28(2):132-137.

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20. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. *Catheter Cardiovasc Interv.* May 1 2007;69(6):910-919.

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Appendix C: Declaration of Helsinki

Accessed: February 9, 2009.
http://www.wma.net/e/policy/b3.htm

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

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

A. INTRODUCTION

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

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

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

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

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

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

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current

interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

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

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

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

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

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

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

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

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

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

Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

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

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

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

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

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

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

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

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

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be

given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

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

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

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

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

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

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly

available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

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

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

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

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

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

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

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

Appendix D: Protocol Revisions

Revision Level	Change Order	Description of Changes
1.0		Initial Release
2.0		Changes made to reduce number of subjects, revise inclusion/exclusion criteria, and change study sponsor to Covidien from ev3.
3.0		Updated number of subjects to 108 enrolled subjects in the protocol synopsis, Section 1.0 Introduction, and Section 5.0 Statistical Method . Appendix A has also been updated to reflect new Medtronic Contact Information.
3.1		Protocol revision: • Protocol version updated to version 3.1 • Protocol version date updated to 17November2016 • Updated Table 9, Approximation to Possible Outcomes and Corresponding 97.5% Lower Confidence Bound. • Formatting to remove blank tables. • Added table header (table 10) to Sample Size Freedom from Stent Fracture table, and updated all table numbers.