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

Statistical Analysis Plan Version 2.0
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Statistical Analysis Plan

Clinical Investigation Plan Title	**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**
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1.   Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	▮▮▮, Principal Statistician
2.0	• Updated this SAP to reflect the new SOP template and Protocol Version 3.1. Added Section 4 Study Objectives, Section % Investigation Plan, Section 6 Determination of Sample Size, Section 7 Statistical Methods and Section 9 Reference.	▮▮▮, Principal Statistician

2.   List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigation Plan
PG	Performance Goal
SAP	Statistical Analysis Plan
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

3.   Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Medtronic Durability PAS Study. The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, this Plan has the following purpose: To prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the clinical evaluation objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the Final Study Report for the overall Clinical Investigational Plan (CIP).

4.   Study Objectives

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 through three years post-procedure.

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:

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

   o   Class 0 – No strut fractures

   o   Class I – Single tine fracture

   o   Class II – Multiple tine fractures

   o   Class III – Stent fracture(s) with preserved alignment of the components

   o   Class IV – Stent fracture(s) with mal-alignment of the components

   o   Class V – Stent fracture(s) in a trans-axial spiral configuration

   AND the following categories:

   o   Category A – Restenosis $\leqslant$ 50% at site of fracture

   o   Category B – Restenosis > 50% at site of fracture

   o   Category C – Occlusion at site of fracture

   o   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.

5.   Investigation Plan

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.

6.   Determination of Sample Size

Primary Endpoint and Sample Size Adjustment

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.[1, 2] 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 1). However, there were no long-term follow-up to 3 years reported.

Table 1: 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)**

Three-year data on freedom from TLR was presented on the PTA arm of the RESILIENT study.[3] 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 2 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.

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%

Table 2: Approximation to Possible Outcomes and Corresponding 97.5% Lower Confidence Bound**Primary Endpoint (PG=35%)**

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 π_t = 0.55 (estimated from current DURABILITY II data), π_{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 3: 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.

7.   Statistical Methods

7.1 Study Subjects

7.1.1   Disposition of Subjects

The number of subjects who are selected, and who have a scheduled follow-up visit will be summarized at each scheduled visit.

7.1.2   Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be reported descriptively by counts of type and listing by site.

7.1.3   Analysis Sets

All study subjects with non-missing values will be included in the primary endpoint analysis and secondary endpoint analysis.

7.2   General Methodology

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.

7.3   Center Pooling

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 case report 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.

7.4   Handling of Missing Data and Dropouts

In general, imputation of missing data will not be performed for all analyses. Subjects who dropped out will be censored at date of last follow-up contact.

7.5   Demographic and Other Baseline Characteristics

All demographic, medical history and clinically relevant baseline variables will be summarized and tabulated. Descriptive statistics will be presented as follows:

- Categorical variables, including binary variables, will be reported by giving the number and percentage of patients in each category.
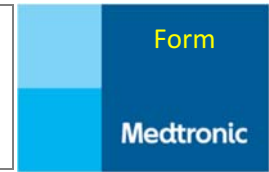
- Continuous variable will be reported by presenting the number of observations, mean, standard deviation, median, IQR, minimum, and maximum of each variable

7.6   Treatment Characteristics

Device success defined as the ability to deploy the stent as intended at the treatment site will be reported.

7.7   Evaluation of Objectives

Analysis of the primary 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.

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.

7.8   Safety Evaluation

All Adverse Events (AEs) will be coded using pre-specified AE Code in the CEC charter. The AEs will be adjudicated by CEC. Frequencies and percentages of AEs will be presented.

7.9   Changes to Planned Analysis

There is no change to the planned analysis. Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

8.   Validation Requirements

	Objectives	Validation level (Level I; Level II)
Primary Endpoint		

	Objectives	Validation level (Level I; Level II)
	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.	Dataset = Level I, Graph=Level II
Secondary Endpoints		
	1.Freedom from Stent Fracture	Dataset = Level I, Graph=Level II
	2. Freedom from acute death, freedom from amputation and freedom from clinically driven target lesion revascularization at 1 and 2 years	Dataset = Level I, Graph=Level II
	3. Freedom from 36-month amputation	Dataset = Level I, Graph=Level II
	4. Freedom from 36-month clinically-driven target lesion revascularization	Dataset = Level I, Graph=Level II
	5. Freedom from acute death	Dataset = Level I, Graph=Level II
	6. Device Success	Level I
	7. Improvement in Rutherford Clinical Category at 1 Year	Level I
	8. Improvement in Ankle-Brachial Index at 1 Year	Level I
	9. Walking Improvement at 1 Year	Level I

	Objectives	Validation level (Level I; Level II)
	10. Adverse Event Rates	Dataset = Level I, Table=Level II
Baseline Demographic and Lesion Characteristic		
	Baseline Demographic and Lesion Characteristic	Dataset = Level I, Table=Level II
Follow up Compliance		
	Follow up compliance	Dataset = Level I, Table=Level II
Protocol Deviation		
	Protocol Deviations	Dataset = Level I, Table=Level II

9.　References

1.　Rocha-Singh KJ. Proposed Performance Goals for Single-Arm Clinical Trials of Bare Nitinol Stents in the Femoral Popliteal Artery. *Vascular InterVentional Advances*. Las Vegas, NV2006.

2.　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.

3.　Katzen B. Long-Term RESILIENT Data for Nitinol Stenting in the SFA. *Vascular Interventional Advances (VIVA)*. Las Vegas2011.