Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	ABRE Study: A multi-center, non-randomized study to evaluate the safety and effectiveness of the Abre venous self-expanding stent system in patients with symptomatic iliofemoral venous outflow obstruction.
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0, 12/DEC/2016	• New Document	Pei Li, Prin Statistician
2.0, 12/JUL/2017	• PMA will be submitted to FDA when all 12-month follow-up data are available. All references to "PMA will be submitted to FDA when the evaluable data are available". Applicable sections are 7.1.3 and 7.6.1. • Time-to-event analyses for primary patency and MAE through 12-month are added. Applicable sections are 7.3.2. and 7.8. • Race/Ethnicity covariates are added for center pooling and multiple imputation. Application sections are 7.5 and 7.6.1. • Patients inclusion restriction is added in section 6.3.	Pei Li, Prin Statistician
3.0, 13/DEC/2019	• Updated the SAP template using 056-F286 vA • Updated SAP content per CIP V1.4 • Updated covariates list for center pooling and multiple imputation 7.3 and 7.4.1 • Added analysis method for secondary endpoints 7.9.3Updated primary patency composite endpoint determination rule 10.3.2.2 • Clarified thrombosis and stent migration, confirmed by core lab imaging, are treated as clinical/safety events; the algorithm for thrombosis and stent migration updated • Added primary assisted patency and secondary patency algorithms 10.3.2.3 • Added analysis window for unscheduled clinic visit 10.3.3	Pei Li, Prin Statistician
4.0, 14/FEB/2020	• Correction of Version date for Version 3 in Summary of Changes Table. There is no content change.	Pei Li, Prin Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
aDVT	Acute deep vein thrombosis
CD-TLR	Clinically-driven target lesion revascularization
CEAP	Clinical Etiologic Anatomic Pathophysiologic
CEC	Clinical Events Committee
CI	Confidence Interval
CIP	Clinical Investigation Plan
DSMB	Data Safety Monitoring Board
DS	Diameter stenosis
DUS	Duplex ultrasound
DVT	Deep vein thrombosis
IVC	Inferior Vena Cava
IVUS	Intravascular Ultrasound
MAE	Major adverse event
NIVL	Non-thrombotic Iliac Vein Lesion
PG	Performance Goal
PTS	Post Thrombotic Syndrome
TLR	Target lesion revascularization
UCL	Upper Confidence Limit
VCSS	Venous Clinical Severity Score
VTE	Venous Thromboembolism

3. Introduction

The ABRE Study will evaluate the safety and effectiveness of the Abre™ venous self-expanding stent system (Abre stent) in patients with symptomatic iliofemoral venous outflow obstruction. The collected data will be used to support regulatory applications in seeking market approval for the stent in the United States and potentially other geographies, as well as presentations and publications.

The study is designed to meet Performance Goals (PGs) established via review of the clinical venous stent literature. The primary endpoints are as follows: a 30-day post-procedure Major Adverse Event PG of 12.5% for safety and a 12-month post-procedure Primary Patency PG of 75% for effectiveness.

A maximum of 200 implanted subjects from up to 35 sites worldwide are planned to be included in the study. Data from 160 subjects are needed to evaluate the primary effectiveness endpoint of primary patency at 12 months, and data from 193 subjects are needed to evaluate the primary safety endpoint of major adverse events at 30 days. A minimum of 40% of included subjects will be from the US. A maximum number of 40 subjects will be included per site (20% of the total study population).

The sample size includes correction for 20% lost-to-follow-up on the effectiveness endpoint and 3.5% lost-to-follow-up on the composite safety endpoint. The sample size is driven by the primary effectiveness and safety endpoints and based on a one-sided alpha of 0.025 and at least 80% overall study power.

A Premarket Approval application will be submitted to FDA when all available 12-month follow-up data have been collected.

4. Study Objectives

The primary objectives of the study are to evaluate primary patency at 12 months and primary safety within 30 days of implanting the Abre stent in patients with symptomatic iliofemoral venous outflow obstruction. Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures.

5. Investigation Plan

This is a prospective, interventional, non-randomized, single arm, multi-center, worldwide study, with each center following a common protocol. A Data Safety Monitoring Board (DSMB) will evaluate safety data during the course the study. A Clinical Events Committee (CEC) will identify clinical events requiring adjudication as specified in the CEC Manual of Operations. The CEC will regularly evaluate and adjudicate these events.

5.1 Inclusion and Exclusion Criteria

Study Inclusion Criteria

1. Patient is ≥ 18 and ≤ 80 years of age;
2. Patient has at least one of the following clinical manifestations (i.e. symptoms and/or signs) of venous disease in lower extremity:
   a. CEAP score ≥ 3 [1]
   b. Venous Clinical Severity Score pain score (VCSS) ≥2
   c. Suspected deep vein thrombosis (DVT);
3. Patient is willing and capable of complying with specified follow-up evaluations at the specified times;
4. Patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the appropriate Ethics Board.

[1] Patients subject to the literature review are similar to the subjects that will be included in the study as more than 90% of the patients in the literature review were classified as CEAP 3 or higher.

Imaging-based Inclusion Criteria

5. Patient has diagnosis of non-malignant venous obstruction within the common iliac, external iliac, and/or common femoral vein. The proximal point of the obstruction may extend to the iliac venous confluence of the inferior vena cava and the distal point may be at or above the deep femoral vein. Diagnosis must be made based on objective imaging by using venography and/or intravascular ultrasound (IVUS). Patient must have good inflow involving either the femoral or deep femoral vein being patent and at least a caudal section of the common femoral vein that is free of significant disease;
6. Patient has an obstructive lesion defined as:
   i. Occluded, or
   ii. ≥50% in diameter reduction on venography or IVUS, or
   iii. ≥50% area reduction on IVUS

7. Acute DVT patients should be treated with the Abre stent within 14 days after onset of symptoms. Patients with acute DVT must first undergo successful treatment of acute thrombus; successful treatment is defined as 30% or less residual thrombus by venogram, as determined by physician, no bleeding, no symptomatic pulmonary embolism (confirmed by imaging), and no renal compromise (renal compromise defined as GFR<30). Patients with underlying obstructive lesions can then be included in the study within the same procedure;
8. Target vessel can accommodate a 9F Sheath, from insertion site to target segment;
9. Exchangeable guidewire must cross target lesion(s) with successful predilation.

General Exclusion Criteria

1. Patient with DVT in the target limb of which the onset of symptoms is between 15 days and 6 months prior to planned treatment or patient has an acute DVT anywhere else than in the target vessel;
2. Patient has peripheral arterial disease-causing symptoms in target limb;
3. Patient is pregnant (female patients of child-bearing potential must have a pregnancy test done within 7 days prior to the index procedure);
4. Patient has a known or suspected systemic infection at the time of the index procedure;
5. Patient has a planned percutaneous or surgical intervention within 30 days prior or 30 days following index procedure, or a contralateral iliofemoral lesion requiring planned treatment within 12 months;
6. Patient requires femoral endovenectomy and patch venoplasty, greater saphenous vein ablation, and/or small saphenous vein stripping during the index procedure;
7. Patient has an active vasculitic inflammatory disorder (e.g. Behcet disease) predisposing the patient to thrombosis and requiring systemic corticosteroid therapy;
8. Patient has impaired renal function (GFR < 30) or is on dialysis;
9. Patient has a platelet count < 50,000 cells/mm^3 or > 1,000,000 cells/mm^3 and/or a WBC < 3,000 cells/mm^3 or > 12,500 cells/mm^3;
10. Patient has a history of bleeding diathesis or either a history or presence of heparin-induced thrombocytopenia antibodies;
11. Patient has a known hypersensitivity or contraindication to antiplatelets or anticoagulation, nitinol, or a contrast sensitivity that cannot be adequately pre-medicated;
12. Patient has presence of other severe co-morbid conditions, which in the investigator's opinion may interfere with the patient's compliance with study visits and procedures, or may confound interpretation of study data (e.g. congestive heart failure Class III and IV, non-ambulatory patients, severe hepatic dysfunction, life expectancy < 1 year);
13. Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures. Patient must be able to consent for themselves;
14. Patient is currently participating in another investigational drug or device study or observational competitive study.

Imaging-based Exclusion Criteria

15. Patient has a vena cava obstruction or lesion extending into the inferior vena cava (IVC), or the presence of bilateral iliofemoral venous lesions requiring planned treatment within 12 months;
16. Patient has significant venous bleeding, arterial dissection or other injury requiring additional percutaneous or surgical intervention prior to enrollment;
17. Patient has a previously placed stent in the ipsilateral venous vasculature;

18. Patient has disease that precludes safe advancement of the venous stent to the target lesion(s).

5.2 Subject Category

Enrolled – not included

Consented subjects who do not meet all I/E criteria will not be treated with the Abre stent. This might be based on the outcome of imaging during the implant procedure. If subjects leave the study before the implant date, safety assessments stop at the date of screening failure. If subjects are excluded based on failing the I/E criteria during the implant procedure, they will be followed for 30 days for safety assessment only. No imaging needs to be sent to the core laboratory for these subjects.

Included

Consented subjects who meet all study-specific I/E criteria will be treated with the Abre stent. During the study procedure, the point at which the Abre system enters the vasculature will be considered the point of inclusion into the study. Subjects who are implanted with the Abre stent will be followed for the duration of the study. Two hundred (200) subjects will be included in this study.

Included – not implanted

This is a sub-category of the Included group. Consented subjects who meet all study-specific I/E criteria will be treated with the Abre stent. During the study procedure, the point at which the Abre system enters the vasculature will be considered the point of inclusion into the study. Those subjects who are not implanted with the Abre stent will be followed for 30 days for safety assessment only. These subjects will be included in the primary analysis set. The pre-procedure/pre-stenting imaging must be submitted to the core laboratory.

5.3 Study Purpose

Protocol-required evaluations are to be performed at the investigative study site by authorized study staff. The collected data will be used to support regulatory applications in seeking market approval for the Abre stent in the United States, and potentially other geographies.

In the US, this study is a pre-market study using investigational product. Outside the US, the study is a post-market study. A common protocol will be followed at all investigational sites. Once included, subjects will remain in the study through completion of the required follow-up duration (or if the stent is not implanted through 30 days), unless the subject withdraws consent, the Investigator withdraws the subject for the subject's best medical interest, or Medtronic terminates the study for any reason.

The enrollment phase is anticipated to last approximately 13 months. The follow-up duration for each subject is 36 months. The total expected duration of the study is approximately 5 years.

6. Determination of Sample Size

6.1 Performance Goal: Primary Effectiveness Endpoint

The primary effectiveness PG endpoint in this study is primary patency. The statistical hypothesis on this endpoint is that primary patency through 12 months will exceed a PG established from historical literature references using venous stenting as the treatment of choice. Formally, the null and alternative hypotheses to be tested appear below:

$$H_0: \pi \leq PG$$
$$H_A: \pi > PG$$

where π is the primary patency at 12 months in the study population and PG is the performance goal, which is calculated as follows. An extensive and independent review of the available literature produced references on venous stenting in similar patient populations. These data are derived from published studies of venous stenting which measured target vessel patency as an endpoint. To estimate the expected rate of primary patency in the study population at 12 months, the review of the available literature was used (see ABRE CIP Appendix A).

Based on the literature, the weighted mean expected primary patency was 85.7%. By subtracting a margin of indifference of 10% from expected performance (85.7% - 10% = 75.7%); consequently, the value of 75% is therefore taken as the PG for the current study. A margin of 10% has been commonly used for primary patency.

For analysis of the imaging component of primary patency, if a subject has both a valid venogram and DUS during the 12-month follow-up period then the venogram will be used. If no venogram is available, then the DUS will be used.

Further details regarding the analysis algorithm for primary patency are found in Appendix A.

6.2 Performance Goal: Primary Safety Endpoint

The study's primary safety endpoint is a MAE composite at 30 days post index procedure. The review of the literature that provided results on these endpoints suggests an expected rate of 5.6% (see Appendix A of CIP). It should be noted that considerably less data, compared to primary patency, was found for the components of this composite endpoint. Therefore, due to the greater uncertainty, a relatively larger margin of indifference was used of 6.8% giving a PG of 12.5%. Formally, the null and alternative hypotheses to be tested appear below:

$$H_0: P \geq PG$$
$$H_A: P < PG$$

where P is the primary safety endpoint at 30 days in the study population and PG is the performance goal.

6.3 Sample Size Calculation

Primary Effectiveness: Using the assumptions above on the PG and anticipated outcome, we assume desired power of at least 92% under hypothesis testing relative to the performance goal at a one-sided alpha of 0.025. The resulting evaluable sample size required is then 160 subjects using exact binomial

test for a single proportion. Accounting for attrition during follow-up, the sample size is augmented by 20% to 200 subjects. Every effort will be made, however, to minimize loss to follow-up.

Primary Safety: Using the assumptions above on the performance goal and anticipated outcome, we assume desired power of at least 92% under hypothesis testing relative to the PG at a one-sided alpha of 0.025. The resulting evaluable sample size required is then 193 subjects using exact binomial test for a single proportion. Accounting for attrition during follow-up, the sample size is augmented by 3.5% to 200 subjects. Every effort will be made, however, to minimize loss to follow-up.

In summary, the overall power of the study is at least 84% while the effectiveness and safety PGs and the projected rates needed to achieve them are as follows:

Table 1: Effectiveness and Safety Performance Goals

Endpoints	PGs	Required rates to pass PG*
Primary Patency at 12 months	75%	81.9% or higher
MAE at 30 days	12.5%	7.8% or lower

*based on projected evaluable sample size

Sample Size calculation for primary patency and primary safety were done using software PASS 2008.

Primary Patency:
Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Exact Test

		Equiv.	Actual	Baseline				
		Proportion	Proportion	Proportion	Target	Actual		Reject H0
Power	N	(P0)	(P1)	(PB)	Alpha	Alpha	Beta	If R>=This
0.9288	160	0.7500	0.8570	0.8570	0.0250	0.0247	0.0712	131

Primary Safety:
Test Statistic: Exact Test

		Equiv.	Actual	Baseline				
		Proportion	Proportion	Proportion	Target	Actual		Reject H0
Power	N	(P0)	(P1)	(PB)	Alpha	Alpha	Beta	If R<=This
0.9233	193	0.1250	0.0560	0.0560	0.0250	0.0249	0.0767	15

6.4 Patient Inclusion

The study Performance Goals (PGs) are based on literature review (see ABRE CIP v1.4 Appendix A Scientific Literature Search). The distribution of patients in literature on which our PGs are based are:

- Acute Deep Vein Thrombosis (aDVT) – 26%
- Nonthrombotic iliac vein lesion (NIVL) – 30%
- Postthrombotic syndrome (PTS) – 44%
-

During the course of the study, Medtronic may limit enrollments to specific indications (i.e. aDVT, PTS, or NIVL), if needed in order to achieve a distribution that is similar to the literature review used to develop the study PGs.

During the course of the study, Medtronic will constantly monitor the enrollment of patients in each category and, once the maximum number of patients included in a category is reached, Medtronic will inform the sites to stop the inclusion of those patients. The pre-defined maximum number of included subjects in each category is:

- aDVT: 31% = 62 included subjects
- NIVL: 35% = 70 included subjects
- PTS: 49% = 98 included subjects

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The subject clinical follow-up compliance at each time will be provided at 30 days, 6, 12, 24 and 36 months via a flow diagram.

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

The primary analysis set will consist of all 'included' subjects who were enrolled and had the Abre system introduced into the vasculature. In general, all analyses will be performed using all evaluable subjects for primary effectiveness and safety analyses (evaluable subject definitions provided below). The point of enrollment for this study is once the subject has been consented and signed and dated the informed consent form. If the Abre system does not enter the vasculature, the subject is considered 'enrolled – not included' and will be followed for 30 days for safety assessment, but will not be included in the primary analysis set. In the case that the Abre stent entered the vasculature in a consented subject but the subject failed to have the study stent implanted, they will be followed for 30 days and exited from the study. These subjects will be considered 'included – not implanted' and will be part of the primary analysis set. The PMA primary analysis will occur when all 12-month follow-up data have been collected.

For the primary effectiveness endpoint, the primary analysis set will be 'included' subjects who are considered evaluable if:
(a) the subject experiences at least one clinically-driven target lesion revascularization within 390 days; or (b) the subject has occlusion or restenosis ≥50% of the stented segment of the target lesion confirmed by core laboratory at 12 months visit; or (c) the subject has at least 330 days follow up without an event in the primary effectiveness endpoint.

For the primary safety endpoint, the primary analysis set will be 'included' subjects who are considered evaluable if:
(a) the subject experiences at least one of the primary safety composite events within 30 days; or (b) stent-migration and stent thrombosis within 30 days are confirmed by imaging as assessed by core

laboratory; or (c) the subject has at least 23 days of clinical follow up without an event in the primary safety endpoint.

Secondary analyses for primary safety endpoint will be conducted on all implanted subjects in which the denominator for the primary safety endpoint will be the number of implanted subjects who had enough follow up (at least 23 days for 30-day follow-up visit) plus any subjects who had an event prior to the milestone visit.

Subject outcomes will be compared qualitatively to outcomes in patients with iliofemoral venous obstruction after medical management alone, based on historical data as reported in the literature.

7.2 General Methodology

Descriptive statistics of continuous characteristics/outcomes will be presented and include sample size, mean, median, standard deviation, minimum, and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented. Subject data listings and tabular and graphical presentations of results will be provided.

One-sided statistical tests will have p-values less than 0.025 deemed significant while two-sided tests will have p-values less than 0.05 deemed significant. Equivalent confidence intervals will also be utilized. Statistical analyses will be conducted in SAS version 9.4 or above (SAS Institute, Cary, N.C.) or another validated statistical software package.

Further details on data handling and analysis are found in Appendix A.

7.3 Center Pooling

Poolability of data across clinical study sites is justified on a clinical basis (i.e. all study sites use the same protocol) the sponsor monitors the site for protocol compliance, and the data gathering instruments are identical. The Food and Drug Administration also requires a statistical assessment of poolability. This is done by comparing the baseline characteristics across study sites. For categorical baseline variables such as gender, a generalized Fisher's exact test or equivalent test will be used and for quantitative variables, parametric or non-parametric analysis of variance (general linear models or an equivalent procedure) will be used.

The above statistical analyses do not result in an impediment to pooling, but rather assess the balance of baseline covariates across study sites. If any baseline covariate is found to be statistically significant by this process, multivariate analyses will be done to determine if the imbalance affected study outcome. This is done by using both the variable found out of balance and study site as possible covariates.

It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. Sites with fewer than 6 subjects will be ranked by enrollment from low to high. Starting from the lowest enrollment site, sites will be combined into a pseudo site until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 6 subjects. This will be done in a manner to preserve the structure of the study and prevent bias.

Because the ABRE Study is being conducted in the US and outside the US (OUS), an analysis will be undertaken to determine if the study sites within the US and OUS subsets are homogeneous in the baseline covariates. The statistical tests used will be the same as those discussed for site poolability.

Baseline characteristics to be considered as possible covariates are as following:

- Age
- Gender
- Race
- Ethnicity
- Chronic Obstructive Pulmonary Disease (COPD)
- Previous history of venous thromboembolism
- Venous Claudication
- Hyperlipidemia
- Known family history of DVT
- Pulmonary embolism
- Thrombophilia
- Peripheral Artery Disease (PAD)
- Hypertension
- Diabetes
- Smoking status
- Villalta score
- VCSS
- Venous disease category (aDVT vs. PTS vs. NIVL)

Poolability analysis will also be performed on the primary endpoints comparing across sites and geographical regions after adjusting for covariates difference. Logistic regression model will be utilized to include unbalanced covariates and site as an independent variable, and the study outcome as dependent variable to assess outcome difference. If the p-value of site effect is less than 0.10, further analyses will be undertaken to investigate the imbalance of the study outcome.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

7.4.1 Multiple Imputation

For primary effectiveness endpoint, primary analysis will be performed using all evaluable data. Multiple imputation will be performed as sensitivity analysis to assess the robustness of the study data to the missing endpoints. For subjects not evaluable for primary effectiveness endpoint, the multiple imputation will be carried out using the logistic regression approach for a dichotomous outcome using PROC MI in SAS for subjects not experiencing the event and not having endpoint data for at least 330 days of follow up.

The following variables will be included in the multiple imputation model as covariates:

- Age
- Gender
- Race
- Ethnicity
- Diabetes
- Venous Disease catergory (aDVT vs. PTS vs. NIVL)
- Villalta score

- VCSS
- Reference Vessel Diameter
- Lesion length

If there are relatively few missing data points (<10%) for a given baseline variable, a simple gender-specific imputation using the mean (for continuous variables) or median (for dichotomous or categorical variables) of the non-missing values will be done. If there are >10% missing, the variable will be excluded from the imputation analysis. Five data sets will be imputed from these covariates and will mimic different realizations of the missing data. For the endpoint, the numerator (the numerator is the point estimate of the treatment for the effectiveness endpoint) and its relevant standard error (the pooled standard error of treatment for the effectiveness endpoint) will be pooled across the 5 data sets using established variance-adjustment methods (e.g., via PROC MIANALYZE in SAS) to create one overall numerator and denominator. The point estimate and the lower bound of the one-sided 97.5% pooled CI will be presented and compared to the primary analysis and the effectiveness PG

7.4.2 Tipping Point Analyses

The Tipping Point method will be adopted to further evaluate study primary objectives by assessing the impact of missing or unknown outcome data on study results. Tipping point analysis results for both primary effectiveness endpoint and primary safety endpoint will be reported.

7.5 Adjustments for Multiple Comparisons

No adjustment for multiple comparisons is needed for this study as both primary endpoints need to be passed for study success.

7.6 Demographic and Other Baseline Characteristics

Demographic (e.g. age, gender, race, etc.) and other baseline characteristics will be summarized descriptively.

7.7 Treatment Characteristics

Procedural characteristics, concomitant therapies and medications will be summarized descriptively.

7.8 Interim Analyses

No interim analysis is planned which would be intended to alter the study sample size or terminate the study early.

7.9 Evaluation of Objectives

7.9.1 Primary Effectiveness Endpoint

Primary Patency is defined as meeting all of the following criteria at 12 months post-procedure:

- Freedom from occlusion[1] of the stented segment of the target lesion;
- Freedom from restenosis[2] ≥50% of the stented segment of the target lesion;
- Freedom from clinically-driven[3] target lesion revascularization[4]

[1,2]All subjects will undergo DUS assessments for determination of patency.
An additional venogram must be performed when:
(1) DUS assessment is suggestive of ≥50% restenosis or occlusion per investigator assessment, or
(2) when DUS is non-diagnostic or suboptimal such as when a patient is obese (e.g. with a BMI >40), or
(3) is clinically required, or in other words when the patient is having symptoms of venous disease in the target limb requiring a venogram. All DUS and venographic imaging examinations will be analyzed by respective independent core laboratories.
[3]Clinically driven is defined as the recurrence of symptoms present at baseline or the onset of new symptoms including, but not limited to venous pain, swelling, dermatitis, or ulceration related to the target limb.
[4]Clinically driven target lesion revascularization will be adjudicated by the CEC based on core laboratory adjudicated imaging data and relevant clinical information provided by the site.

7.9.1.1 Hypothesis Testing

The primary effectiveness endpoint in this study is primary patency rate. The statistical hypothesis on this endpoint is that primary patency through 12 months will exceed a performance goal established from historical literature references using venous stenting as the treatment of choice. Formally, the null and alternative hypotheses to be tested appear below:

$$H_0: \pi \leq PG$$
$$H_A: \pi > PG$$

where π is the primary patency rate at 12 months in the study population and PG is the performance goal of 75%.

7.9.1.2 Statistical Method

The primary patency rate is calculated as the number of subjects without loss of primary patency divided by the number of subjects having evaluable primary endpoint data for primary patency rate at 12 months.

Based on the literature (see ABRE CIP Appendix A Scientific Literature Search), the weighted mean expected primary patency was 85.7%. By subtracting a margin of indifference of 10% from expected performance (85.7% - 10% = 75.7%); consequently, the value of 75% is therefore taken as the performance goal for the current study. The 12-month patency rate and lower limit of the 97.5% one-sided confidence interval will be reported. The primary effectiveness objective will be met if the lower limit of the 97.5% one-sided confidence interval of the 12-month patency rate is above 75%.

For the primary effectiveness endpoint, subjects will be included in the analysis and considered evaluable if:
(a) the subject experiences at least one clinically-driven target lesion revascularization within 390 days; or (b) the subject has occlusion or restenosis ≥50% of the stented segment of the target lesion confirmed by core laboratory at 12 months or (c) the subject has at least 330 days follow up without an event in the primary effectiveness endpoint.

For analysis of the imaging component of primary patency, if a subject has both a valid venogram and DUS during the 12-month follow-up period then the venogram will be used. If no venogram is available,

then the DUS will be used. This is an imaging endpoint. More details of the reporting rules are used to determine this endpoint can be found in section 10.3.2.

Further, as supportive analysis on the primary endpoints, time-to-event analysis for primary patency through 12 months will also be performed and serves as a secondary analysis. Kaplan-Meier (KM) estimates with 95% two-sided confidence interval using Peto formula will be reported for primary patency rate through 360 days as well as 390 days to accommodate the 12-month visit window. Subjects not experiencing the event by 12 months will be censored at 12 months or last known follow-up as defined in Appendix A, whichever is earlier. Subjects not experiencing the CD-TLR but experiencing the Target Vessel Revascularization (TVR) before 12-month imaging window will be censored at date of TVR when evaluating the 12-month primary effectiveness endpoint. The imaging assessment for such subjects that are available either on or before the TVR date, if within the 12-month reporting window, may still be used.

Sensitivity analyses for primary effectiveness endpoint include multiple imputation and tipping point analysis which are further explained in section 7.4.

7.9.2 Primary Safety Endpoint

The primary safety endpoint of this study will be the incidence of composite Major Adverse Events (MAE) at 30 days following stenting of an obstruction in the iliofemoral venous segment. MAEs will be adjudicated by a Clinical Events Committee (CEC), except for stent thrombosis and stent migration as they are confirmed by core laboratory.

The components of the 30-day MAE composite include:

- All-cause death occurring post-procedure
- Clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism
- Major bleeding complication (procedural)
- Stent thrombosis confirmed by imaging as assessed by core laboratory
- Stent migration confirmed by imaging as assessed by core laboratory

Note: Migration excludes stent dislodgement at the index procedure as may occur with under-sizing of a stent.

More details of the reporting rules are used to determine this endpoint can be found in section 10.3.1.

7.9.2.1 Hypothesis Testing

The review of the literature that provided results on the composite MAE endpoint components suggests an expected rate of 5.6% (see ABRE CIP Appendix A Scientific Literature Search). It should be noted that considerably less data, compared to primary patency, was found for the components of this composite endpoint.

Therefore, due to the greater uncertainty, a relatively larger margin of indifference was used of 6.8% giving a performance goal of 12.5%. Formally, the null and alternative hypotheses to be tested appear below:

H_0: P ≥ PG
H_A: P < PG

where P is the rate of the composite primary safety endpoint at 30 days in the study population and PG is the performance goal of 12.5%.

7.9.2.2 Statistical Method

The primary safety failure rate is calculated as the number of subjects who had a major adverse event within 30 days divided by the number of evaluable subjects who had enough follow up (at least 23 days for 30-day visit) plus any subjects who had a major adverse event within 30 days. Primary safety failure rate and the exact one-sided 97.5% upper confidence limit (UCL) will be reported. The primary safety objective will be met if the exact one-sided 97.5% UCL is below 12.5%.

For the primary safety endpoint, subjects will be included in the analysis and considered evaluable if:

(a) the subject experiences at least one of the primary safety composite events within 30 days, or
(b) stent migration and/or stent thrombosis within 30 days confirmed by imaging as assessed by core laboratory, or
(c) the subject has at least 23 days of clinical follow up without an event in the primary safety endpoint.

Tipping point analysis for primary safety endpoint as sensitivity analysis is mentioned in section 7.4.2.

7.9.3 Secondary Endpoints

To assess how the subjects are doing clinically, the following secondary endpoints will be evaluated. All secondary endpoints will be evaluated using descriptive statistics. No inferential analyses are planned. Detailed analysis methods for core laboratory endpoints and endpoints assessed by office visits can be found in Section 10.

In addition, time-to-event analysis will be performed and Kaplan Meier (KM) estimates with two-sided 95% confidence interval using Peto formula will be reported for major adverse events (MAE) and its component events through 12 months, and annually through 36 months.

Acute success secondary endpoints

1. **Device success:** Successful delivery and deployment of the Abre stent in the target lesion with successful removal of the delivery system.

2. **Lesion success:** Venographic evidence of <50% final residual stenosis of the stented segment of the target lesion after post-dilation, when applicable, and as assessed by core laboratory.

3. **Procedure success:** Lesion success without procedure-related MAEs prior to hospital discharge within 30 days.

   Note: If core laboratory is unable to assess the venographic evidence, site reported data will be used.

Late success secondary endpoints

4. **Primary Assisted Patency at 12 months:** Uninterrupted patency of the stented segment of the target lesion with a secondary intervention, also known as an adjunctive treatment (e.g. balloon venoplasty, subsequent stenting, etc.).

5. **Secondary Patency at 12 months:** Patency of the stented segment of the target lesion after subsequent intervention for an occlusion.

6. **Target Lesion Revascularization (TLR) through 30 days, 6-, 12-, 24- and 36 months:** Any reintervention of the stented segment of the target lesion.

7. **Major Adverse Events (MAE) through 6-, 12-, 24- and 36 months:** MAEs include:
   - All-cause death occurring post-procedure
   - Clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism
   - Major bleeding complication (post-procedural)
   - Stent thrombosis confirmed by imaging as assessed by core laboratory
   - Stent migration confirmed by imaging as assessed by core laboratory
     Note: Migration excludes stent dislodgement at the index procedure as may occur with undersizing of a stent

   All MAEs will be adjudicated by a CEC, except for stent thrombosis and stent migration as they are confirmed by core laboratory.

8. **Delayed Stent Migration at 12-, 24-, and 36 months:** position change of a venous stent observed with an imaging modality > 1 cm from its original location at the conclusion of the index procedure, as determined with regard to a reference anatomic structure.

9. **Stent Fracture at 30 days, 12-, 24- and 36 months:**
   Fracture or breakage of any portion of the stent.
   Determined by X-ray for the first 30 subjects at 30 days and for all subjects (including the first 30 subjects) at 12-, 24- and 36 months using the following classifications (36) as adjudicated by a venous stent fracture core laboratory:
   i. Type 0 – No strut fractures
   ii. Type I – Single tine fracture
   iii. Type II – Multiple tine fractures
   iv. Type III – Stent fracture(s) with preserved alignment of the components
   v. Type IV – Stent fracture(s) with mal-alignment of the components
   vi. Type V – Stent fracture(s) in a trans-axial spiral configuration

10. **Change in VEINES-QOL/Sym Score at 6-, 12-, 24- and 36 months:** Defined as the change in VEINES-QOL/Sym score at 6, 12, 24, and 36 months compared to baseline.

11. **Change in VILLALTA Score at 6-, 12-,24-, and 36 months:** Defined as the change in VILLALTA score at 6, 12, 24, and 36 months compared to baseline.

12. **Change in EQ5D Quality of life Score at 6-, 12-, 24-, and 36 months:** Defined as the change in Quality of Life Score as assessed by EQ5D questionnaire at 6, 12, 24, and 36 months compared to baseline.

13. **Change in VCSS Score at 6-, 12-, 24-, and 36 months:** Defined as the change in VCSS Score at 6, 12, 24, and 36 months compared to baseline.

14. **Major bleeding complication at 30 days, 6-, 12-, 24- and 36 months:** A blood loss leading to transfusion of whole blood or red cells provided hemoglobin drop of 3 g/dL (1.86 mmol/L) or more is related to bleeding occurring during the index procedure through 36 months post-index procedure.

15. **Medical resource utilization through 36 months** including length of stay and re-hospitalizations.

Secondary Endpoint Analysis Method

Secondary Endpoint	Endpoint Category
1. Device success	Clinical/Safety Endpoint
2. Lesion success	Core Laboratory Endpoint
3. Procedure success	Clinical/Safety Endpoint
4. Primary Assisted Patency at 12 months	Imaging + Clinical/Safety Endpoint
5. Secondary Patency at 12 months	Imaging + Clinical/Safety Endpoint
6. Target Lesion Revascularization (TLR) through 30 days, 6-, 12-, 24- and 36 months	Clinical/Safety Endpoint
7. Major Adverse Events (MAE) through 6-, 12-, 24- and 36 months	Clinical/Safety Endpoint
8. Delayed Stent Migration at 12-, 24- and 36 months	Imaging Endpoint
9. Stent Fracture at 30 days, 12-, 24- and 36 months	Imaging Endpoint
10. Change in VEINES-QOL/Sym Score at 6-, 12-, 24- and 36 months	Endpoint Assessed by Clinic Visit
11. Change in VILLALTA Score at 6-, 12-, ,24-, and 36 months	Endpoint Assessed by Clinic Visit
12. Change in EQ5D Quality of life Score at 6-, 12-, 24-, and 36 months	Endpoint Assessed by Clinic Visit
13. Change in VCSS Score at 6-, 12-, 24-, and 36 months	Endpoint Assessed by Clinic Visit
14. Major bleeding complication at 30 days, 6-, 12-, 24- and 36 months	Clinical/Safety Endpoint
15. Medical resource utilization through 36 months including length of stay and re-hospitalizations.	Clinical/Safety Endpoint

7.10 Safety Evaluation

For adverse events (AEs), serious adverse events (SAEs), major adverse events (MAE) and Unanticipated Adverse Device Effects (UADEs) reporting, the primary analysis will be based on subject counts, not event counts. The subject counts and the percentages will be presented in tabular summaries of results. Reporting of laboratory finding will be reported descriptively.

7.11 Health Outcomes Analyses

VEINES-QOL/Sym score, VILLALTA score, VCSS and EQ5D Quality of Life score change from baseline to 6,12, 24, and 36 months will be reported for this study.

7.12 Changes to Planned Analysis

Any changes to the analysis plan will be documented in Clinical Study Report with the reason for the change.

8. Validation Requirements

Statistical analysis will be validated using double programming for all study endpoints.

9. References

There were no references needed for this SAP.

10. Statistical Appendices

Appendix A – Data Handling and Analysis Incomplete Data

If a date needed for calculation is an incomplete date (e.g. **112006 or ****2006) it will be completed as follows:

For incomplete event dates '01' or '0101' will be entered, respectively (worst case).

However, if an imputed event date is before date of procedure, the date of event will be set equal to the date of procedure.

For all other incomplete dates '15' or '01JUL' will be entered, respectively (less far from correct date). If the missing month is known to be between July and December, the month September will be used.

If the entire start date of an event is missing the index procedure date will be imputed.

10.1 Follow-up Visit Windows

Follow-up assessments will be done at:

Day 0 = day of procedure	Type of follow-up
30 days – 7 days/+ 14 days	Clinic Visit
6 mo ± 30 days	Clinic visit
12 mo ± 30 days	Clinic visit
24 & 36 mo ± 30 days	Clinic visit

The date for the 30-day follow-up should be calculated by adding 30 days to the index procedure date (e.g. treatment on December 5th, 30 day follow up on January 4th). The dates for the 6-, 12-, 24-, and 36 months follow-up assessments should be calculated using the anniversary date of the index procedure (e.g. procedure on December 5th, 6-month follow up on June 5th, 12 month and annual thereafter on December 5th). If the procedure was performed on the 31st and the follow-up month has only 30 days, the anniversary should be calculated to the first day of the next month. Visit window calculations will be provided for each subject through the EDC system.

10.2 General Analysis Definitions

Assessments will be presented chronologically by study day, which is defined in the following:

Study day = assessment day – date of index-procedure.

Index-procedure day = 0. Events occurring on the day of the index-procedure will be considered day 0.

Note: if the staged procedure is 14 days post index-procedure and an event occurs on this day this event will be reported on day 14 even if it is clearly attributed to the staged procedure.

Events occurring on the day of discharge will be considered in-hospital.

Time of follow-up = date of last contact – date of index procedure. where date of last contact includes but not limited to date of death or the latest of: (1) date of last adverse event, (2) date of last image, (3) date of last procedure, (4) date of last scheduled or unscheduled -follow-up visit, (5) date of Study Exit.

Events will be reported up to the number of months times 30. So, for 6 months 6*30=180 days will be used, and for 12 months or 1 year, 360 days will be used. For analysis at each time point, subjects will be censored at the time point or time to follow-up as defined above, whichever is earlier.

For all the clinical/safety endpoints, the denominator will include subjects who either have an adjudicated event (e.g. death, revascularization) before the time of interest, or have a contact beyond the lower window of the follow-up.

10.3 Specific Reporting Conventions

Three types of endpoints will be reported – Clinical/safety endpoints, Imaging endpoints, and endpoints assessed by clinic visit. The reported windows are specified for each type of the endpoints below.

10.3.1 Clinical/Safety Endpoints

Clinical/safety endpoints include repeat revascularization procedure on target lesions/vessels and safety endpoints including MAEs (composite and individual components). Most of the event rates of the clinical/safety endpoints will be calculated on patient basis and for different reporting time points, the corresponding cutoff days will be used: 30 days for 30-day; 180 days for 6-month; 360 days for 12-month; 720 days for 24-month; and 1080 days for 36-month.

For each visit (or reporting time point), the event rate will be calculated as the proportion of number of subjects with certain event term over the number of evaluable subjects, the denominator of the event rate calculation will be event specific. The evaluable subjects at each reporting time point include all subjects who are included by the snapshot date and

1) Had an event within (on or before) the reporting cutoff days, or
2) Had a follow-up at or after the lower limit of the reporting window, or
3) The withdrawal consent date/recorded lost-to-follow-up date at or after the lower limit of the reporting window

'Days to event' (date of earliest event – date of index procedure) and 'Days to last contact' (date of last contact – date of index procedure) are usually used for the determination of the eligibility of the 'evaluable subject'. The last contact date will be calculated based on the information gathered from all available dates during the follow-ups.

The 'Reporting Cutoff Days', 'Lower limit of the Reporting Window' and the correspondent visits are as the following:

Table 2. Reporting Cutoffs for Clinical/Safety endpoints

Visit	Reporting Cutoff Days	Lower Limit of the Reporting Window (days post-index procedure)
30 days	30 days post-index procedure	Days to last contact: 23
6-month	180 days post-index procedure	Days to last contact: 150
12-month	360 days post-index procedure	Days to last contact: 330
24-month	720 days post-index procedure	Days to last contact: 690
36-month	1080 days post-index procedure	Days to last contact: 1050

Other AE/SAEs that are recorded during the study will be reported on the standard safety population, i.e. all included subjects.

<u>For 30-day primary safety endpoint</u>

The components of the 30-day MAE composite endpoint include:

- All-cause death occurring post-procedure
- Clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism
- Major bleeding complication (procedural)
- Stent thrombosis confirmed by imaging as assessed by core laboratory
- Stent migration confirmed by imaging as assessed by core laboratory

The following Table 3 specifies how individual component events are determined:

Table 3. Individual Component Event Determination For 30-Day Safety Endpoint

Primary Safety Endpoint Component Events	Data Source	Event Failure	Individual Endpoint Derivation Rules	Composite Endpoint Derivation Rules
All-cause death	CEC	**Event within 30 days post-index procedure by CEC adjudication**	**Numerator**: event-specific, e.g. number of subjects with all-cause death within 30-day post index procedure, will be the numerator for 30-day all-cause death event rate calculation; **Denominator**: event specific denominator includes any subjects with the event, or subjects had no event but had at least 23-day of clinical follow-up	**Numerator**: number of subjects with at least one of these five events within 30 days post-index procedure; **Denominator**: *evaluable* subjects – any subjects with at least one of these five events, or subjects had none of these five events but had at least 23-day of clinical follow-up
Clinically significant pulmonary embolism	CEC			
Major bleeding complication (procedural)	CEC			
Stent thrombosis	Imaging-Confirmed	**Stent thrombosis or migration within 30 days post index-procedure, confirmed by Venogram imaging**		
Stent migration	Imaging-Confirmed			

10.3.2 Imaging/Core Laboratory Endpoints

The imaging/core laboratory endpoints include the following:

1. Restenosis (≥50% restenosed of the stented segment of the target lesion) or Occlusion (100% occluded of the stented segment of the target lesion). The imaging assessments are adjudicated by DUS core laboratory or venography core laboratory where applicable;
2. Stent Fracture - assessed by x-ray core laboratory;
3. Delayed Stent Migration (position change of a venous stent observed with an imaging modality >1 cm from its original location at the conclusion of the index procedure, as determined with regard to a reference anatomic structure) - assessed by x-ray or Venography core lab

10.3.2.1 Imaging Reporting Window

Imaging will be considered qualified by completion of the corresponding scheduled visit. For those subjects that missed the scheduled visit, the following reporting windows will be applied to qualify the unscheduled visit, if applicable. The study day used in following Table 5 for the window definitions is calculated as "assessment date" minus "Index procedure date":

Table 4. Imaging reporting window

Study Visit	Target Day	Reporting Window
Index Procedure	Day 0	NA
30-Day	Day 30	NA
6-Month	Day 180	NA
12-Month	Day 360	Study Day 271 – 420

Study Visit	Target Day	Reporting Window
24-Month	Day 720	Study Day 421 – 780
36-Month	Day 1080	Study Day 781 – 1140

10.3.2.2 Primary Patency

Primary Patency Composite Endpoint Determination

Primary Patency has two components:

1. CD-TLR
2. Imaging endpoint of Occlusion/Restenosis

Primary patency endpoint determination will follow the rules described below:

1. Censor any imaging assessments or events after any TVR (not clinically driven) as this changes the vessel making the subject unevaluable for patency at 12 months. If the date of assessment > date of TVR, then set the value to 'missing'
2. All Subjects that had CD-TLRs within 390 days will be counted as Primary Patency Failure whether or not an imaging assessment is available after the CD-TLR event. Subjects with TVR (not clinically driven) before the CD-TLR will be censored.
3. The imaging component of the 12-month primary patency will be constructed based on 'AT' principle – prior events will not be carried over to a later visit. For each subject, qualified imaging assessment will be determined in the following order:
    a. Venogram on scheduled 12-month visit regardless of window.
    b. DUS on scheduled 12-month visit regardless of window
    c. Venogram from unscheduled visit within the imaging window, choose the one closest to the target visit date if there are multiple
    d. DUS on unscheduled visit within the imaging window, choose the one closest to the target visit date if there are multiple

Primary Patency at 24 months, and 36 months follow-up will be determined following the similar convention specified above for 12 months.

For each individual component of the primary patency endpoint, the rate will be calculated in the following way:

The proportion rate of CD-TLR will be constructed as a clinical/safety endpoint - number of subjects with CD-TLR over number of evaluable subjects through the cutoff of a reporting time point. For example, for 12-month CD-TLR under the primary patency endpoint, the cutoff to determine the numerator is 390 days – this includes any subjects who had their first CD-TLR within 390 days. The denominator will be all subjects that had CD-TLR or had no CD-TLR but had at least 330 days of clinical follow-up.

The CD-TLR Endpoint will be reported cumulatively.

The determination of imaging component of the occlusion/restenosis endpoint is described above.

10.3.2.3 Primary Assisted Patency/Secondary Patency

The primary assisted patency and secondary patency endpoints are specified below in Table 5.

Table 5. Primary Assisted Patency and Secondary Patency Endpoints

Outcome Scenarios	Primary Patency	Primary Assisted Patency	Secondary Patency
Patent (DUS, Venogram) at 12 months, no CD-TLR and no TLR before 12 months	Success	Success	Success
Binary Restenosis/Occluded (DUS, Venogram) at 12 months, and no TLR (not clinically driven) before 12 months	Failure	Failure	Failure
TLR (not clinically driven) before 12 months, before any CD-TLR , before 12 month imaging	Missing	Missing	Missing
Patent Venogram, DUS) at 12 months, CD-TLR before 12 months due to restenosis but no occlusion	Failure	Success	Success
Patent (Venogram, DUS) at 12 months, CD-TLR before 12 months due to occlusion	Failure	Failure	Success
Image missing at 12 months, CD-TLR before 12 months due to restenosis but no occlusion	Failure	Missing	Missing
Image missing at 12 months, CD-TLR before 12 months due to occlusion	Failure	Failure	Missing

10.3.2.4 Stent Fracture/Delayed Stent Migration

These endpoints are reported by core laboratory imaging. The proportion rate of these endpoints will be constructed cumulatively on both stent level and subject level.

Numerator: subject/stent with any positive findings determined by scheduled visits and unscheduled image from day 0 to the upper limit of the imaging reporting window specified in Table 4.

Denominator: all *qualified* subjects/stents at a given visit – all subjects/stents with completed and evaluable imaging as part of the scheduled visit, or with unscheduled imagingwithin the imaging reporting window specified for that visit (all imaging data should be evaluable), plus subjects/stents with positive findings before that timepoint.

10.3.3 Endpoints Assessed by Clinic Visit

Endpoints assessed by clinic visit include EQ5D VCSS Scores, etc. These assessments/endpoints are obtained/determined through the clinic visit assessment. If the clinic visit (scheduled and unscheduled) is not completed then these assessments will not be available, and therefore will be treated as missing values and will be excluded from the analysis.
For the assessments that are recorded on the scheduled visit forms regardless of window, the scheduled visit data will be used in the analyses.

For subjects that don't have any assessment for a scheduled visit (visit not done or the visit is completed but the assessment is not readable), the following rules will be used to slot the unscheduled visit assessments:

1.) Assessments will be slotted into each study visit (including scheduled and unscheduled visit) using the visit date, visit window is described in Table 6.

2.) The assessments with unevaluable values will be excluded from the visit slotting step;

Table 6. Endpoints by Clinic Visit Reporting Window

Study Visit	Target Day	Reporting Window
Index Procedure	Day 0	NA
30-Day	Day 30	NA
6-Month	Day 180	Study Day 91 – 270
12-Month	Day 360	Study Day 271 – 420
24-Month	Day 720	Study Day 421 – 780
36-Month	Day 1080	Study Day 781 – 1140

If multiple assessments are slotted into the same visit window, the assessment with non-missing value that is closest to target visit date will be used. If multiple non-missing assessments have equal distance from the target visit date, the assessment from the earlier assessment will be used.