Medtronic

# 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.

Clinical Investigation Plan (CIP)

CIP IDENTIFIER: APV – ABRE

ClinicalTrials.gov Identifier: NCT03038438

IDE number: G160163/A001

VERSION 1.4

24/SEP/2018

# 1 Version History

| Version | Summary of changes | Author(s)/title |
|---|---|---|
| *1.0*<br>*28/JUN/2016* | Not applicable, new document | Myriam Demas / Principal Clinical Research Specialist |
| *1.1*<br>*21/Nov/2016* | ○ Administrative updates<br>○ Synopsis: Expected First Enrollment changed to '2017'<br>○ Major Bleeding definition updated<br>○ Inclusion Criteria 6, ii updated: IVUS added<br>○ Inclusion Criteria 7: successful treatment of acute DVT patients specified<br>○ Exclusion Criteria 9 updated: upper limit for WBC added<br>○ Medication: Statins information added to be collected<br>○ Section 10: clarifications added to procedures<br>○ 10.12.1: Clarification added to Antiplatelet treatment<br>○ 10.12.5: Pregnancy test specified<br>○ 10.12.7: Physical assessment of limbs specified<br>○ 14.2 power adapted according to results of updated literature search<br>○ 14.3 Populations specified<br>○ 14.4 Statistical tests for primary endpoints specified<br>○ 14.3 Evaluable data specified<br>○ 14.6 Handling missing data specified<br>○ 14.7 Poolability assessment specified<br>○ Section 18: clarification added to Justification for the Study<br>○ Appendix A: updated scientific literature search | Myriam Demas / Principal Clinical Research Specialist |
| *1.2*<br>*06/APR/2017* | ○ Administrative updates<br>○ Front page: ClinicalTrials.gov Identifier and IDE number added.<br>○ Removed reference to Good Clinical Practice in "Investigator Statement" and "Glossary" as the ABRE study will follow the good clinical practice principles as outlined in ISO14155.<br>○ "Synopsis - Lead Principal Investigators": address of Dr. Erin Murphy updated.<br>○ The Abre stent system has obtained CE mark. | Myriam Demas / Clinical Research Manager |

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| | All references to “CE mark will be obtained” updated accordingly. Applicable sections are: “Synopsis”, “7. Study Design”, “8.1.2 Abre Stent Delivery System”.<br>o “Synopsis - Expected first enrollment” updated to 2017.<br>o 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” updated accordingly. Applicable sections are: “Synopsis - Statistics” and “14.3 Analysis Sets”.<br>o “Race / ethnicity” data are collected in this study. Rationale provided in the “Background” section. Race and Ethnicity information added/updated in the following sections: “10.3.1 Demographics, Medical History & Physical Examination”, “14.6 Handling of Dropouts and Missing Data”, “14.7 Assessment of Data Pooling” and “14.8 Minimizing Bias”.<br>o “7.2 Rationale”: rationale added for single-arm study design.<br>o “9.3 Subject Screening” and “10.15 Table 8”: Enrolled subjects do not need to be recorded on the Subject Screening Log. They will only be recorded on the Subject Identification & Enrollment Log.<br>o “9.4 Inclusion Criteria”: renal compromise specified.<br>o Duplex ultrasound image of the contralateral limb is required. All applicable sections updated. These are “10.6 Hospital Discharge”, “10.7 30 Day (-7/+14 days) Post-Procedure Follow-Up Assessment”, “10.8 6 Months (± 30 days) Post-Procedure Follow-Up Assessment”, “10.9 12 Months (± 30 days) Post-Procedure Follow-Up Assessment”, 10.10 24 and 36 Months (± 30 days) Post-Procedure Follow-Up Assessment”, “10.11 Unscheduled Visits”, “10.12.6 Imaging”.<br>o “10.12.7 Physical Assessment of Limbs”. Changed ‘diameter of the leg” to “diameter of the thigh” and “presence of lymphedema” added.<br>o “11.2 Potential Benefits”. Added potential benefit for participation in the study. | |

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| | ○ "Appendix C CEAP Classificiation": correction made (LSV changed to SSV). | |
| *1.3a*<br>*31/JUL/2018* | ○ Administrative updates<br>○ "Synopsis – Sample Size". Added 'implanted' to following statement - "A maximum of 200 implanted subjects will be included in the study".<br>○ "Synopsis – Sample Size". Changed from the maximum number of OUS subjects will not exceed 50% to "A minimum of 40% of included subjects will be from the US".<br>○ "Synopsis – Estimated Time Course and "7.1 Duration". Updated 'Expected First Enrollment' to 'First Enrollment – 19/DEC/2017' and changed 'Expected Enrollment Duration' from '17' to '13' months.<br>○ "Synopsis – Inclusion/Exclusion Criteria" and "9.4 Inclusion Criteria" following language added to Imaging-based inclusion criterion #5: "Patient must have good inflow involving either the femoral or deep femoral vein being patent and at aleast a caudal section of the common femoral vein that is free of significant disease".<br>○ "Synopsis – Inclusion/Exclusion Criteria" and "9.4 Inclusion Criteria" following language deleted from Imaging-based inclusion criterion #7: "by catheter-based techniques".<br>○ "Synopsis – Inclusion/Exclusion Criteria" and "9.5 Exclusion Criteria" following language removed from exclusion criterion #3: "negative" in relation to pregnancy test and parentheses added around requirement to complete a pregnancy test within 7 days prior to the index procedure.<br>○ "Synopsis – Study Procedures and Assessments" and "10.1 Table 6" clarification added to 'Screening/baseline' window to indicate assessments should be completed <30 days "before procedure".<br>○ "Synopsis – Study Procedures and Assessments" and "10.1 Table 7" language added to footnote 1 stating "If both screening and pre-procedure venogram/IVUS are performed, then the pre-procedure venogram/IVUS should be sent to the core laboratory. | Stephanie Brucato / Principal Clinical Research Specialist |

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| | ○ "6.3.1 Primary Endpoints – Primary safety endpoint" clarification added to indicate MAEs will be adjudicated by a CEC "except for stent thrombosis and stent migration as they are confirmed by core laboratory".<br>○ "6.3.2 Secondary Endpoints - #7 Major Adverse Events through 6-, 12-, 24-, and 36 months" clarification added to indicate MAEs will be adjudicated by a CEC "except for stent thrombosis and stent migration as they are confirmed by core laboratory".<br>○ "6.3.2 Secondary Endpoints - #9, #10, #11, and #12" timepoints for analysis extended from 12M out to include 24- and 36 month timepoints.<br>○ "6.3.2 Secondary Endpoints - #14". Added 'through 36 months'.<br>○ "8.7 Product Receipt and Tracking" Device 'serial' number deleted and 'Device lot number' added.<br>○ "9.3 Subject Screening" remove requirement for sites to complete a Subject Screening Log. All applicable sections updated including "Table 5", "Figure 4", and "Table 8".<br>○ "9.3 Subject Screening – Enrolled – not included" added statement "No imaging needs to be sent to the core laboratory for these subjects." Same reference added to footer 4 of "Table 8".<br>○ "9.3 Subject Screening – Enrolled – not implanted" added statement "The pre-procedure/pre-stenting imaging must be submitted to the core laboratory."<br>○ "10.1 Schedule of Events" additional detail added to indicate that the Screening/Baseline Duplex Ultrasound is to be performed on both limbs in parenthesis.<br>○ "10.4 Acute DVT Subjects" minor edits made to section to clarify the requirements.<br>○ "10.5.4 Inflow Requirements" added "significant" in the following sentence: "Good inflow involves either the femoral or deep femoral vein being patent and at aleast a caudal section of the common femoral vein that is free of significant disease."<br>○ "10.5.5 Lesions" added 'iliac' after 'common' in first sentence for clarity.<br>○ "10.5.6 Predilation". Sentence related to | |

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| | predilation updated to clarify that a balloon of the same size diameter of the stent to be implanted must be used.<br>○ "10.5.7 Stent Size Selection – Stent Length". Clarification added to state that the ends of the stents lie in a "relatively" normal/healthy venous segment.<br>○ "10.5.7 Stent Size Selection – Stent diameter". For number 2, specification of AP and 60 LAO for venogram planes removed to correspond to core lab manual.<br>○ "10.5.7 Stent Size Selection – Stent diameter". Clarifications made to section for reference vessel diameter assessment. For all three methods the phrase "an appropriate segment of" has been added to replaceme the previously used phrase "the same anatomical segment".<br>○ "10.5.8 Stent Placement". Following sentence added "Whenever possible, one stent should be used to cover the entire length of the target lesion." And clarification added to section in the event that stents of differing diameters are needed. In this case the following statements were added: "If different diameters are needed, the smaller diameter stent should be placed first." And clarification added to ensure no skip areas.<br>○ "10.12.1 Antithrombotics". Added "bolus of 5000 units or" to second bullet under 'Peri-procedure' section.<br>○ "10.12.3 Scores – Villalta Score" corrected reference to indicate "Villalta" instead of "VCSS" in third sentence.<br>○ "10.12.7 Physical Assessment of Limbs". Corrected 'diameter' of thigh and calf to 'circumference'.<br>○ "Table 8: Overview data collection for different scenarios". Removed requirement to complete 'Procedure' eCRFs for Enrolled – not included subjects who are screening failures during implant procedure.<br>○ "10.15 Recording Data - Source Documents". Exception updated to indicate that select data on the Product Accountability Log may serve as source. Removed example of exception related to quality of life and clinical scores.<br>○ "12.1.1 Definitions – Table 10: Definitions – | |

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| | Unanticipated Serious Adverse Device Effect". Extra language removed to match referenced ISO definition.<br>○ "12.1.2 Classification of Causal Relationships – Table 11". Abre stent implant procedure definition updated to 'Any AE that occurs within 30 days of the Abre stent implant procedure unless specifically shown not to be related to that procedure.'.<br>○ "12.2.1 Evaluation and Documentation of Adverse Events and Device Deficiencies". Clarification added to last paragraph of section to specify that "…*specific* endpoint-related adverse events *as described in the CEC Manual of Operations*…".<br>○ "Table 13: Unavoidable events". Low grade fever '27.8°C' corrected to '37.8°C'.<br>○ "Table 14" Timeframe for reporting Adverse Events changed from 'no later than 10 working days of' to 'In a timeline manner from'.<br>○ "15.1 Statement(s) of Compliance". Reference to 45 CRF Part 11 added.<br>○ "16.5 Site Activation/Supply of Study Materials". Added 'Other relevant documentation for key site staff (i.e. DUS Technicians) is allowable' as sub-bullet to Curriculum vitae requirement.<br>○ "Appendix B Definitions". 'Iliac' added after 'common' to specify 'common iliac' in Target lesion and Target vessel definitions. | |
| *1.3b*<br>*20/AUG/2018* | ○ "Appendix B Definitions". 'Stent migration' definition changed to "Position change of a properly sized venous stent observed with an imaging modality, with displacement of the stent outside of the intended treatment segment after the conclusion of the index procedure, as determined with regard to a reference anatomic structure. Stent migration occurs following the proper deployment of a venous stent after the index procedure (i.e. stent movement or dislodgement during the index procedure will not be noted as stent migration)." | Stephanie Brucato / Principal Clinical Research Specialist |
| *1.3c*<br>*20/SEP/2018* | ○ "Secondary Endpoints". 'Delayed Stent Migration at 12-, 24-, and 36 months' added as secondary endpoint #8. All subsequent secondary endpoint #s updated. | Sue Kim / Sr. Clinical Program Manager |

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| | ○ "Appendix B Definitions". 'Stent migration' definition updated to state that existing stent migration definition is part of the primary safety and secondary MAE endpoints, and 'delayed stent migration' definition added as part of secondary endpoint. | |
| *1.4*<br>*24/SEP/2018* | ○ Update to correct version per internal procedures | Stephanie Brucato / Principal Clinical Research Specialist |

# 2 Investigator Statement

| | |
|---|---|
| **Study product name** | Abre venous self-expanding stent system |
| **Global sponsor** | Medtronic Vascular Inc.<br>3576 Unocal Place<br>Santa Rosa<br>California 95403<br>United States |
| **Local sponsor Europe** | Medtronic Bakken Research Center B.V.<br>CardioVascular Department, Aortic & Peripheral Vascular<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands |
| **Clinical Investigation Plan identifier** | APV - ABRE |
| **Version number/date** | 1.4 / 24SEP2018 |

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with all applicable regulatory guidelines under which the study is being conducted, e.g., United States Food and Drug Administration regulations and International Standard ISO14155. I agree to conduct the study in compliance with country, local and internal institutional requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

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| **Investigator's signature** | |
| **Investigator's name** | |
| **Institution** | |
| **Date** | (DD/MMM/YYYY) |

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# 3 Glossary

| Term | Definition |
|---|---|
| AE | Adverse Event |
| ACT | Activated Clotting Time |
| ADE | Adverse Device Effect |
| CA | Competent Authority |
| CAD | Coronary Artery Disease |
| CBC | Complete Blood Count |
| CEAP | Clinical Etiologic Anatomic Pathophysiologic |
| CEC | Clinical Events Committee |
| CI | Confidence Interval |
| CIP | Clinical Investigation Plan |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPT | Chronic Postthrombotic |
| CRF | Case Report Form |
| CTPA | Computed Tomography Pulmonary Angiography |
| CVA | Cerebrovascular Accident |
| DOAC | Direct Oral Anticoagulants (e.g. Dabigatran, Rivaroxaban, Apixaban, or Edoxaban) |
| DSMB | Data Safety Monitoring Board |
| DUS | Duplex Ultrasound |
| DVT | Deep Vein Thrombosis |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EQ5D | Euro QOL 5 Dimensions |
| FDA | Food and Drug Administration |

| Term | Definition |
|---|---|
| GFR | Glomerular Filtration Rate |
| HBP | High Blood Pressure |
| HDPE | High-Density Polyethylene |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| I/E Criteria | Inclusion and Exclusion Criteria |
| IFU | Instructions for Use |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IVC | Inferior Vena Cava |
| IVUS | Intravascular Ultrasound |
| MAE | Major Adverse Events |
| MDD | Medical Devices Directive |
| MI | Myocardial Infarction |
| NIVL | Nonthrombotic Iliac Vein Lesion |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OTW | Over-The-Wire |
| OUS | Outside the US |
| PAD | Peripheral Artery Disease |
| PEEK | Polyether Ether Ketone |
| PTFE | Polytetrafluoroethylene |
| PG | Performance Goal |
| PHI | Protected Health Information |
| PI | Principal Investigator |

| Term | Definition |
|---|---|
| PVD | Peripheral Vascular Disease |
| PTS | Postthrombotic syndrome |
| QOL | Quality of Life |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SFA | Superficial Femoral Artery |
| SID | Subject Identification Number |
| SVS | Society for Vascular Surgery |
| TLR | Target Lesion Revascularization |
| UADE | Unanticipated Adverse Device Effect |
| US | United States |
| USADE | Unanticipated Serious Adverse Device Effect |
| VCSS | Venous Clinical Severity Score |
| VEINES | Venous Insufficiency Epidemiological and Economic Study |

# 4 Synopsis

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|---|---|
| **Name of Study** | ABRE Study |
| **Title** | 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 |
| **Clinical Study Type** | Pivotal |
| **Product Name** | Abre™ venous self-expanding stent system<br>(hereafter, “Abre stent” in case only the stent is meant, “Abre system” in case the Abre stent including the delivery system is meant) |
| **Global Sponsor** | Medtronic Vascular Inc.<br>3576 Unocal Place<br>Santa Rosa, California 95403<br>United States |
| **Local Sponsor Europe** | Medtronic Bakken Research Center B.V.<br>Cardiac and Vascular Group, Aortic & Peripheral Vascular<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands |
| **Lead Principal Investigators** | **Erin H. Murphy, MD**<br>Division of Vascular and Endovascular Surgery<br>Sanger Heart and Vascular Institute<br>10625 Park Rd.<br>Charlotte, North Carolina 28210<br>United States<br><br>**Stephen Black, MD**<br>Department of Vascular Surgery<br>Guy's & St Thomas' NHS Foundation Trust, St Thomas’ Hospital<br>1 Westminster Bridge Road<br>London, SE1 7EH<br>United Kingdom |
| **Indication under investigation** | The Abre venous self-expanding stent system is intended for use in the iliofemoral veins for the treatment of symptomatic venous outflow |

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| | obstruction.<br>In the United States (US) the device will be investigational and an investigational device exemption (IDE) approval will be obtained before the study is initiated.<br>Outside the US, the device is CE marked. The study will be conducted within the approved indication. |
| **Investigation Purpose** | Evaluate the safety and effectiveness of the Abre venous self-expanding stent system for treatment of symptomatic iliofemoral venous outflow obstruction in patients with venous occlusive disease. The collected data will be used to support regulatory applications to seek market approval in the US and potentially other geographies. |
| **Product Status** | The Abre system is investigational in the US and it is CE marked in countries that require CE.<br>Geographies where CE mark is accepted might participate in the study. |
| **Primary Objective(s)** | The primary objectives are to evaluate effectiveness (i.e. achieving a performance goal of 75% primary patency at 12 months) and safety (i.e. achieving a performance goal of 12.5% incidence of major adverse events within 30 days) of the Abre system in subjects with iliofemoral venous obstruction. |
| **Secondary Objective(s)** | Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures. |
| **Study Design** | This is a prospective, interventional, non-randomized, single arm, multi-center, worldwide study, with each center following a common protocol. |
| **Sample Size** | A maximum of 200 implanted subjects will 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.<br>A minimum of 40% of included subjects will be from the US.<br>A maximum number of 40 subjects will be included per site (20% of the total study population). |
| **Number of sites** | Up to 35 sites worldwide. |
| **Study Population** | Patients between 18 and 80 years (inclusive) requiring treatment of a non-malignant venous obstruction within the common iliac, external iliac and/or common femoral vein. |
| **Follow-up** | Subjects who are implanted with the Abre stent will be followed for 3 years. They will have scheduled follow-up visits at 30-days, 6-, 12-, 24-, and 36-months post index procedure. |

<table>
<tr><td>Estimated Time Course</td><td>
<table>
<tr><th>Activities</th><th>Timeline</th></tr>
<tr><td>First Enrollment</td><td>19/DEC/2017</td></tr>
<tr><td>Expected Enrollment Duration</td><td>Approximately 13 months</td></tr>
<tr><td>Completion of Follow-Up</td><td>3 years, or until study closure</td></tr>
<tr><td>Expected Study Duration</td><td>5 years, or until study closure</td></tr>
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<tr><td>Inclusion/Exclusion Criteria</td><td>
General Inclusion Criteria<br>
1. Patient is ≥ 18 and ≤ 80 years of age;<br>
2. Patient has at least one of the following clinical manifestations (i.e. symptoms and/or signs) of venous disease in lower extremity:<br>
a. CEAP score ≥ 3[1]<br>
b. Venous Clinical Severity Score pain score (VCSS) ≥2 (1)<br>
c. Suspected deep vein thrombosis (DVT);<br>
3. Patient is willing and capable of complying with specified follow-up evaluations at the specified times;<br>
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.<br><br>
Imaging-based Inclusion Criteria<br>
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;<br>
6. Patient has an obstructive lesion defined as:<br>
i. Occluded, or<br>
ii. ≥50% in diameter reduction on venography or IVUS, or<br>
iii. ≥50% area reduction on IVUS
</td></tr>
</table>

[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.

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);<br>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;<br>14. Patient is currently participating in another investigational drug or device study or observational competitive study.<br><br>**Imaging-based Exclusion Criteria**<br><br>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;<br>16. Patient has significant venous bleeding, arterial dissection or other injury requiring additional percutaneous or surgical intervention prior to enrollment;<br>17. Patient has a previously placed stent in the ipsilateral venous vasculature;<br>18. Patient has disease that precludes safe advancement of the venous stent to the target lesion(s). |
| **Statistics** | The study is designed to meet performance goals (PG) established via review of the clinical venous stent literature. A 30-day Major Adverse Event PG of 12.5% and a 12-month Primary Patency PG of 75% in patients with venous occlusive disease are used.<br><br>200 subjects are planned for inclusion. This 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.<br><br>Primary analyses will be conducted after a minimum of 160 subjects have evaluable primary patency data at 12 months to evaluate the primary effectiveness endpoint and 193 subjects have evaluable follow-up data at 30 days to evaluate the primary safety endpoint.<br><br>A Premarket Approval application will be submitted to FDA when all available 12-month follow-up data have been collected. |

**Study Procedures and Assessments**

## Schedule of Assessments and Visit Windows

| Data Collection Requirement | Screening/Baseline (<30 days before procedure unless otherwise specified) | Procedure | Hospital Discharge | 30 Day (-7/+14 days) | 6 Months (± 30 days) | 12 Months (± 30 days) | 24 & 36 Months (± 30 days) | Unscheduled visit for intervention in target vein |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Demographics, Medical History & Physical Exam | X | | | | | | | |
| Pregnancy Test[1] | X | | | | | | | |
| CEAP Classification | X | | | | | | | |
| Physical Assessment of Limbs | X | | X | X | X | X | X | X |
| Villalta Score, VCSS | X | | | X | X | X | X | X[4] |
| VEINES-QOL/Sym, EQ-5D QOL | X | | | | X | X | X | X[4] |
| Procedure Data | | X | | | | | | X |
| Serum Creatinine, CBC | X | | | | | | | |
| INR (if on warfarin) | X | | | X | X | X | X | X |
| Document Adverse Events | X[2] | X | X | X | X | X | X | X |
| Document Device Deficiencies | | X | X | X | X | X | X | X |
| Medication[3] | X | X | X | X | X | X | X | X |
| Discontinuation Information[5] | | | X | X | X | X | X | X |

[1] Pregnancy test for women of child-bearing potential only. Must be done within 7 days prior to the index procedure.

[2] Adverse Event assessment need to be done as of the moment the subject is enrolled in the study (i.e. subject signed and dated the informed consent form).

[3] Medication which will be collected: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins

[4] Assessments and questionnaires should be taken before any intervention.

[5] The discontinuation data is needed whenever the subject ends involvement in the study.

**Schedule of Imaging Assessments and Visit Windows**

| Data Collection Requirement | Screening/Baseline (<30 days) | Procedure | | Hospital Discharge | 30 Day (-7 days, +14 days) | 6 Months (± 30 days) | 12 Months (± 30 days) | 24 & 36 Months (± 30 days) | Unscheduled visit for intervention in target vein |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-stenting | Post-stenting | | | | | | |
| Duplex Ultrasound | X | | | X[2] | X | X | X[4] | X | X |
| Venogram | 1 | X[1] | X | | | | 4 | | X |
| IVUS | 1 | X[1] | X | | | | | | X |
| X-ray | | | | | 3 | | X | X | X[5] |

[1] Diagnosis can be made during the screening/baseline prior to the index procedure based on objective imaging using venography or IVUS. Diagnosis can also be made during the index procedure, prior to stenting. In case venogram and IVUS are not performed pre-stenting at the time of the index procedure, the pre-procedure venogram and IVUS should be sent to the core laboratory. If screening and pre-procedure venogram/IVUS are performed, then the pre-procedure venogram/IVUS should be sent to the core laboratory.[2] The DUS examination immediately after the index procedure needs to be performed between 0 and 7 calendar days from the index procedure. When the first examination after the procedure is non-diagnostic, a second examination has to be performed as soon as possible. Every effort should be made to perform this within 7 calendar days after the index procedure.

[3] X-rays at 30 days will be performed on the first 30 subjects only. They will be assessed for first safety analysis (i.e. stent fracture).

[4] 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 subject is obese (e.g. with a BMI >40 ), or;

(3) is clinically required, or in other words when the subject is having symptoms of venous disease in the target limb requiring a venogram.

[5] Plain x-ray is required pre and post re-intervention to assess for stent fracture.

# 5 Introduction

## 5.1 Background

Iliofemoral venous obstruction has been recognized with increasing frequency as the underlying cause of lower extremity symptoms including edema, pain, skin changes and, in advanced cases, ulceration. When the presentation is that of acute deep venous thrombosis (DVT), swelling and pain predominate. However, in addition to these symptoms, patients with chronic venous obstruction from nonthrombotic or postthrombotic etiologies often have skin and subcutaneous changes which can present as hyperpigmentation, lipodematosclerosis, or venous ulceration. [(2)] The latter pattern of symptoms comprises the postthrombotic syndrome. The etiologic mechanism of the symptoms is two-fold; venous valvular incompetence (reflux) and outflow obstruction. These two mechanisms are interlinked; obstruction can lead to dilatation of veins resulting in valvular incompetence. As well, spontaneous recanalization after venous thrombosis often results in destruction of the valves in the involved segments. The relative contribution of these two mechanisms to the development of symptoms varies from patient to patient, but the best results can be achieved when both reflux and obstruction can be treated. [(3)] [(4)]

The prevalence of chronic iliofemoral outflow obstruction, whether postthrombotic or nonthrombotic, is difficult to discern from the literature. Many live for years with the disease and only seek treatment when the symptoms become incapacitating. For this reason, there is a paucity of strong data on which to base estimates of disease prevalence. An estimate of the size of the population appropriate for iliofemoral venous stenting relies on two assumptions. First, venous stenting is indicated only in patients with significant symptoms (CEAP class C3 or greater). Second, venous stenting is not appropriate for those patients with valvular incompetence as the primary etiology for symptoms, or in those with venous obstruction limited to the femoral and more caudal veins.

Estimates vary for the prevalence of significant (CEAP class C3 or greater) venous disease. For C3/C4 disease, estimates range from 5% to 17%. For C5/C6 disease, estimates range between 1% and 2%. [(5)] [(6)] [(7)] [(8)] Using a midpoint of 12%, the prevalence of C3 – C6 disease is approximately 29 million in the US adult population. Among these, Lurie and colleagues estimate that 90% will manifest iliofemoral venous outflow obstruction. Thus, approximately 25 million patients in the US have iliofemoral venous obstruction of a severity where iliofemoral venous stenting might be appropriate.

Despite the basis of this calculation on a consensus document, many will find this estimate far too high. To approach the problem from a different angle, we consider again the epidemiology study by Criqui, et. al. (2003) [(5).] These authors found that 1.0% prevalence of deep functional disease and trophic changes (C4 - C6 disease). While this excludes C3 patients who might also benefit from stent placement, it also includes patients with deep venous reflux without obstruction, or obstruction in the femoral vein that does not extend into the iliofemoral segment. Assuming that these exclusions and inclusions are approximately equal, the 1.0% estimate suggests that about 2.4 million patients have iliofemoral outflow obstruction suitable for venous stenting. So we conclude that the true prevalence of iliofemoral venous outflow obstruction lies between 2.4 million and 25 million US adults.

The aforementioned estimates do not include those patients appropriate for stenting after acute iliofemoral deep venous thrombosis (DVT). These patients, by and large, have chronic, often asymptomatic iliofemoral venous lesions; lesions unmasked after removing the acute thrombus. Based on US hospital discharge data, approximately 600,000 DVT are diagnosed in the US annually (ICD-9-CM code 453.xx). There are varying estimates of how many of these involve the iliofemoral segment. One recent estimate from [(9)] documented iliofemoral involvement in 38% of patients with DVT.

Discounting the overall estimate for recurrent DVT in the same patients, estimated to be approximately 30% over long-term follow-up, [10] [11] the incidence of acute iliofemoral DVT suitable for stenting is approximately 160,000 per year (600,000 x 38% x 70%).

Even today, most patients presenting with acute iliofemoral DVT are treated with anticoagulation alone. [12] [13] [14] Patients with postthrombotic symptoms are often followed with non-interventional management consisting of compression hose and elevation of the extremity. [11] While effective at preventing pulmonary embolism and recurrent DVT, medical management of symptomatic venous obstruction is associated with the development of debilitating symptoms over long-term follow-up. [15] A variety of definitive modalities have been used to restore venous outflow and alleviate symptoms. For acute DVT, active thrombus removal techniques such as pharmacologic thrombolysis and percutaneous mechanical thrombectomy in combination with venous angioplasty and stenting has emerged as the first line treatment to rapidly re-establish venous patency. [16] [17] [18] [19] Venous stenting has been successfully employed as a stand-alone primary intervention for symptomatic non-acute postthrombotic and nonthrombotic iliofemoral outflow obstruction. [17] [18] [20] [21]

Despite the increasing use of stents for acute DVT, chronic postthrombotic and nonthrombotic venous obstruction, most studies have employed stents originally designed for arteries or for biliary indications. Most publications comprise single-center retrospective series. Prospective, protocol-driven, monitored studies with core laboratory analyses of imaging studies are rare. [22] This observation must be taken into account when assessing the frequency of clinical events; with the possibility of underreporting due to the retrospective nature of data collection.

Currently, there are several societal guideline documents on the standard of care for the treatment of iliofemoral venous lesions. Most of these are heavily weighted toward the treatment of acute DVT. A guideline document published by the American College of Phlebology in October 2015 [23] supplements a 2014 clinical practice guidelines document from the Society of Vascular Surgery and the American Venous Forum for the management of venous leg ulcers, [24] [a]nd other earlier societal guideline documents. [25] [26] [27] While many of the guideline documents are focused on the management of acute thrombotic venous obstruction, some caveats regarding venous stenting have been included. As well, several review articles have been published, some recently, providing some insight to current practice in the field. [28] [29] [30] [31] [32] [33] [34]

Today, venous stenting can be considered as a standard of care for symptomatic, anatomically-significant iliofemoral venous outflow obstruction. [21] [28] [33] Currently, however, no dedicated venous stent is approved for the iliac vein indication in the US, although several are CE marked and marketed outside the US.

### 5.1.1 Literature Review

A scientific literature search has been performed to provide an up-to-date review of published data on the safety and effectiveness of stenting for iliac and iliofemoral venous disease. The review included peer-reviewed publications identified by the web-based search strategy with the National Library of Medicine National Center for Biotechnology Information PubMed resource and Cochrane Library through a search date of October 1, 2016. The substance of the literature review was formed by 63 selected publications. Most publications were single-center, retrospective, non-randomized series. Articles were published between 1996 and 2016 with treatment dates between 1987 and 2014. The reviewed publications outline the clinical and anatomic characteristics of the population of patients with iliofemoral venous obstruction who were medically-managed and/or treated with venous stents and provided the conclusions below.

The average age at presentation was 52.7 years, although patients presented throughout all age ranges. Females presented more often than males; 63.5% versus 36.5%, respectively. Lesions were more often on the left than the right; 70.0% vs. 20.4%. Bilateral lesions were treated in 9.6% of patients. At baseline, two-thirds of patients were within the C3 or C4 CEAP categories; more mild symptomatology was found in only 8.7% of cases; 26.4% presented with a healed (C5, 7.5%) or active ulcerations (C6, 18.9%).

The literature has shown that venous stenting is generally safe. Major hemorrhage occurred in 1.1% of patients with access site hematomas in 3.6%. Other access site complications such as false aneurysms or arteriovenous fistulae were very rare, as was pulmonary embolism or death within 30 days of the procedure; each occurring in 0.2% or fewer patients. When major adverse events (MAE) were defined as the composite occurrence of death, stent thrombosis, pulmonary embolism or stent migration, 5.6% experienced an MAE within 30 days. Stent fracture was reported in only 1.4% of patients, with stent dislodgement (at the index procedure) in 0.6% and stent migration (after the index procedure) in 1.6%.

Effectiveness as measured by patency rate was also satisfactory. At 12 months primary, primary-assisted and secondary patency rates were 85.7%, 93.8% and 95.2%, respectively. Target lesion revascularization (TLR) at 12 months was 8.3%. There did not appear to be substantial differences in outcome between patients treated with off-label or CE marked venous stents, but the relatively small sample for CE marked stents precludes a robust analysis. In summary, iliofemoral venous stenting as reported in the literature appears to be associated with relatively few perioperative and longer-term complications, with a primary patency rate of approximately 85.7% at one year.

The literature shows that angioplasty and venous stenting are safe and effective in patients presenting with acute deep vein thrombosis, chronic postthrombotic syndrome (PTS) and chronic nonthrombotic iliac vein lesion (NIVL). The Abre system was developed specifically for this need. This study will evaluate safety and effectiveness of the Abre system specifically in order to support regulatory submissions in the US and other geographies.

The 63 selected publications on past trials for the target indication (Appendix A Scientific Literature Search) did not report any race and ethnicity-specific prevalence. Although evidence exists that incidence rates of venous thromboembolism (including pulmonary embolism and deep vein thrombosis) show significant variation among different ethnic/racial groups, [35] the prevalence of venous thromboembolism (and more specific iliofemoral outflow obstruction) in different racial and ethnic groups has not yet been thoroughly studied. In the ABRE Study, race and ethnicity data will be collected to improve the completeness and quality of demographic subgroup data to better understand whether there are potentially clinically important racial/ethnic-based differences in the anticipated effect of the intervention.

## 5.2 Purpose

The purpose of this study is to evaluate the safety and effectiveness of the Abre venous self-expanding stent system for the treatment of patients with symptomatic iliofemoral outflow obstruction. The clinical performance of the Abre system will be evaluated through a prospective, single-arm, non-randomized multi-center clinical study in a total of 200 subjects with a hypothesis-based 30-day composite safety endpoint and a hypothesis-based 12-month effectiveness endpoint to be tested against performance goals.

Subjects who are implanted with the Abre stent will be followed for 3 years. With anticipated 20% loss of data on the effectiveness endpoint and 3.5% loss on data on the composite safety endpoint, a Premarket Approval application will be submitted to FDA when all available 12-month follow-up data have been collected, including the data needed to demonstrate primary safety (193 subjects have evaluable follow-up data at 30 days) and primary effectiveness (160 subjects have evaluable primary patency data at 12 months) are obtained.

# 6 Objectives and Endpoints

## 6.1 Primary Objectives

The primary objectives are to evaluate the effectiveness (i.e. achieving a performance goal of 75% primary patency at 12 months) and safety (i.e. achieving a performance goal of 12.5% incidence of major adverse events within 30 days) of implanting the Abre stent in subjects with iliofemoral venous obstruction.

## 6.2 Secondary Objectives

Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures.

## 6.3 Endpoints

### 6.3.1 Primary Endpoints

The primary effectiveness endpoint for this study has been chosen based on the results of an extensive literature review (Appendix A Scientific Literature Search). Individual components of the primary safety composite endpoint have been reported in a number of venous stenting studies.

**Primary effectiveness endpoint**

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

- Freedom from occlusion[2] 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]

[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.

**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.

### 6.3.2 Secondary Endpoints

To assess how the subjects are doing clinically, the following secondary endpoints will be evaluated.

**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]

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

[5] Confirmed by Duplex ultrasound scan evaluated by independent core laboratory. In cases where both DUS and venography were used at the same time point, venography would be used for the primary assessment.

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

7. **Major Adverse Events (MAE) through 6-, 12-, 24- and 36 months:**
   MAEs include:

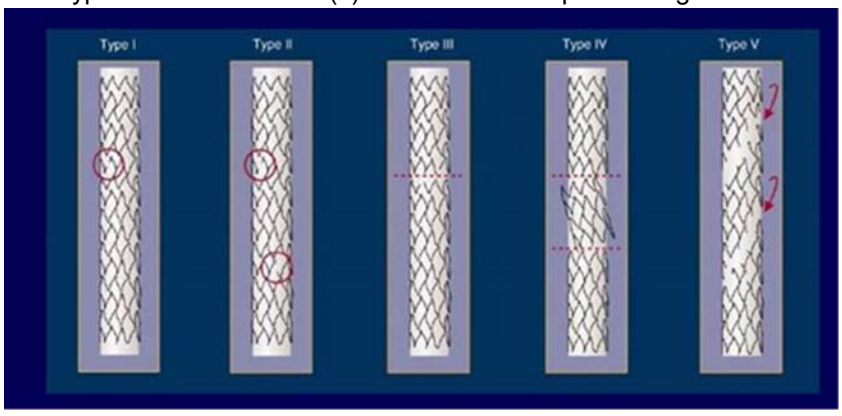
   - All-cause death occurring post-procedure
   - Clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism
   - Major bleeding complication (post-procedural)
   - Stent thrombosis confirmed by imaging as assessed by core laboratory
   - Stent migration confirmed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

   Note: Migration excludes stent dislodgement at the index procedure as may occur with under-sizing 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. [37]

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 136 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.

# 7 Study Design

This is a prospective, interventional, non-randomized, worldwide, multi-center study, to assess the safety and effectiveness of the Abre venous self-expanding stent system in subjects with symptomatic lliofemoral venous outflow obstruction with each site following a common protocol. A maximum of 200 subjects will be included at up to 35 sites in the US and selected countries outside of the US. The maximum number of subjects included outside the US will not exceed 50% of the total number of included subjects. The participating sites and principal investigators will be listed in a separate overview, which is maintained in the Trial Master File and Investigator Site File. To avoid introduction of bias to the study results due to disproportionate inclusion, the maximum number of subjects included per site will be no more than 40 (or 20% of the total study population). Study-wide, 200 subjects will be implanted with one or more Abre stent(s). A minimum of 200 stents will be used during the study. However, a subject can receive more than one stent when needed. It is expected that the average subject will require 1 or 2 stents. Refer to the IFU for additional device use and sizing details. Subjects who are implanted with the Abre stent will be evaluated at baseline, procedure, hospital discharge, 30 days, 6 months, and annually thereafter through 3 years or until study closure. Protocol-required evaluations will be performed at the investigative study sites by authorized study staff. The collected data will be used to support regulatory applications in seeking market approval for the Abre system in the US, and potentially other geographies.

In the US, this study is a pre-market study using investigational product in the US. Outside the US, the study is a post-market study. A common protocol will be followed at all investigational sites.

## 7.1 Duration

Once included, subjects will remain in the study through completion of the required follow-up duration, 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.

## 7.2 Rationale

The clinical performance of the Abre system will be evaluated through a prospective, single-arm, non-randomized multi-center clinical study in a total of 200 included subjects with a hypothesis-based 30-day composite safety endpoint and a hypothesis-based 12-month effectiveness endpoint derived from performance goals. The study has been designed to meet a primary patency performance goal of 75% and a safety performance goal of 12.5% to achieve study success.

An extensive scientific literature review (Appendix A Scientific Literature Search) was undertaken with the objective to provide an up-to-date review of published data on the safety and effectiveness of stenting for iliac and iliofemoral venous disease.

Critical appraisal of the information collected in the literature review established a 30-day post-procedure composite MAE rate and a 12-month post-procedure primary patency rate in order to assess respectively the safety and effectiveness of the Abre system.

The design is single-arm since (1) no gold standard exists to treat iliofemoral vein obstruction and (2) "medical treatment alone" cannot assess the effectiveness endpoint of primary patency of the stented segment, meaning comparisons are not relevant.

Significant pre-clinical testing via bench and animal models along with research feasibility activities have been performed to ensure product quality and optimize system performance. This study will evaluate the safety and effectiveness in subjects.

# 8 Product Description

## 8.1 General

The Abre system is intended for use in the iliofemoral veins for the treatment of symptomatic venous outflow obstruction.

The Abre system consists of a stent and stent delivery system designed specifically for implantation in the peripheral venous system. The Abre system consists of a flexible self-expanding stent made of a nickel-titanium alloy (nitinol) provided in multiple lengths and diameters and an over-the-wire stent delivery system. **Table 1** lists the stent diameters and lengths for the Abre stent.

**Table 1: Stent Diameters and Lengths**

| | | Stent Length (mm) | | | | | | Nitinol Tube Wall Thickness |
|---|---|---|---|---|---|---|---|---|
| | | 40 | 60 | 80 | 100 | 120 | 150 | |
| Stent Diameter (mm) | 10 | x | x | x | x | x | x | 0.018” |
| | 12 | | x | x | x | x | x | |
| | 14 | | x | x | x | x | x | |
| | 16 | | x | x | x | x | x | 0.028” |
| | 18 | | x | x | x | x | x | |
| | 20 | | x | x | x | x | x | |

### 8.1.1 Stent

The Abre stent is a flexible self-expanding nitinol (nickel-titanium alloy) stent provided in multiple lengths and diameters. The stent is laser machined from a continuous seamless piece of nitinol tubing into an open lattice design.

A drawing of the laser cut Abre stent is seen in **Figure 1.** There are no welds, joints, or bonds used in the construction of the stent. The Abre stent cell geometry includes three wave peaks between connection bridges. An alternating off-line pattern used for the connection bridges is intended to increase stent flexibility. The Abre stent is designed for durability. Compound radii were applied to specific nodes in order for high strain locations to be further reduced resulting in a higher fatigue life. These radii can be seen in the figures below. After being laser cut, the stent is electropolished and passivated. The Abre stent uses integral nitinol markers for visibility. **Figure 2** is a picture of the finished stent. Upon deployment, the stent achieves its predetermined diameter and exerts an outward force to maintain patency and placement (i.e. no migration) in the target vessel.

Cell lengths and strut widths vary linearly with stent diameter across two groups of stent diameters:

(1) the 10-14 mm diameter stents, which are cut from a starting tube thickness of 0.018”; and
(2) the 16-20 mm diameter stents, which are cut from a starting tube thickness of 0.028”.

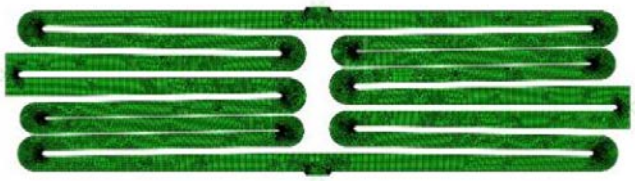


**Figure 1: Abre laser cut pattern**

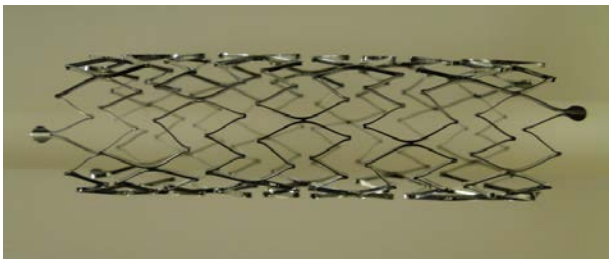


**Figure 2: Abre finished stent**

### 8.1.2 Abre Stent Delivery System

The Abre stent delivery system is an over-the-wire (OTW), 9 Fr, 0.035” guide wire compatible, delivery system for deploying the Abre self-expanding nitinol stent in the iliofemoral vein. The catheter is a triaxial shaft configuration consisting of an inner shaft, a retractable sheath, and an isolation sheath. The inner shaft is PEEK (polyether ether ketone) with a radiopaque Pebax tip. The retractable sheath is a braid reinforced nylon with a PTFE liner. The isolation sheath is High-Density Polyethylene (HDPE). The retractable sheath has one 90% Platinum/10% Iridium radiopaque marker that aids in positioning the catheter. The isolation sheath is attached to the deployment handle assembly via the strain relief. A single luer port is located on the proximal end of the deployment handle. Saline is injected into this port to flush air from the system. The handle assembly contains a thumbwheel actuated deployment mechanism that, along with the isolation sheath, provides control and accuracy during stent deployment. A locking pin prevents the stent from being deployed prior to intended use and must be removed to actuate the thumbwheel.

As the thumbwheel is rotated, a stainless steel Pull Cable is wound onto the thumbwheel and pulls the retractable sheath toward the handle, deploying the stent.

**Figure 3** provides a drawing of the Abre stent delivery system.

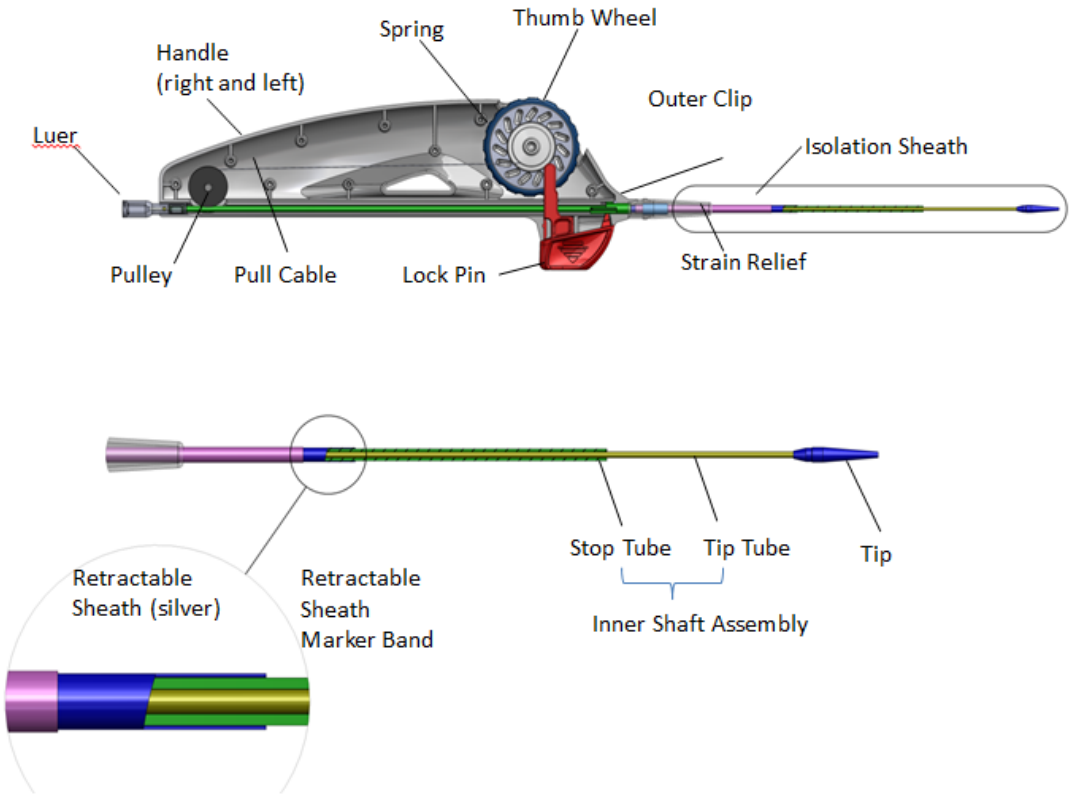



**Figure 3: Abre stent delivery system**

Abre system model numbers are listed in **Table 2** for the US and  for outside the US. In the event model numbers are added to the study, an updated model number list will be made available separate from this CIP.

**Table 2: Abre system model numbers in US**

| Model | Stent Ø (mm) | Stent Length (mm) | Working Length (cm) |
|---|---|---|---|
| AB9T10040090 | 10 | 40 | 90 |
| AB9T10060090 | 10 | 60 | 90 |
| AB9T10080090 | 10 | 80 | 90 |
| AB9T10100090 | 10 | 100 | 90 |
| AB9T10120090 | 10 | 120 | 90 |
| AB9T10150090 | 10 | 150 | 90 |
| AB9T12060090 | 12 | 60 | 90 |
| AB9T12080090 | 12 | 80 | 90 |
| AB9T12100090 | 12 | 100 | 90 |
| AB9T12120090 | 12 | 120 | 90 |
| AB9T12150090 | 12 | 150 | 90 |
| AB9T14060090 | 14 | 60 | 90 |
| AB9T14080090 | 14 | 80 | 90 |
| AB9T14100090 | 14 | 100 | 90 |
| AB9T14120090 | 14 | 120 | 90 |
| AB9T14150090 | 14 | 150 | 90 |
| AB9T16060090 | 16 | 60 | 90 |
| AB9T16080090 | 16 | 80 | 90 |
| AB9T16100090 | 16 | 100 | 90 |
| AB9T16120090 | 16 | 120 | 90 |
| AB9T16150090 | 16 | 150 | 90 |
| AB9T18060090 | 18 | 60 | 90 |
| AB9T18080090 | 18 | 80 | 90 |
| AB9T18100090 | 18 | 100 | 90 |
| AB9T18120090 | 18 | 120 | 90 |
| AB9T18150090 | 18 | 150 | 90 |
| AB9T20060090 | 20 | 60 | 90 |
| AB9T20080090 | 20 | 80 | 90 |
| AB9T20100090 | 20 | 100 | 90 |
| AB9T20120090 | 20 | 120 | 90 |
| AB9T20150090 | 20 | 150 | 90 |

**Table 3: Abre system model numbers outside the US**

| Model | Stent Ø (mm) | Stent Length (mm) | Working Length (cm) |
|---|---|---|---|
| AB9G10040090 | 10 | 40 | 90 |
| AB9G10060090 | 10 | 60 | 90 |
| AB9G10080090 | 10 | 80 | 90 |
| AB9G10100090 | 10 | 100 | 90 |
| AB9G10120090 | 10 | 120 | 90 |
| AB9G10150090 | 10 | 150 | 90 |
| AB9G12060090 | 12 | 60 | 90 |
| AB9G12080090 | 12 | 80 | 90 |
| AB9G12100090 | 12 | 100 | 90 |
| AB9G12120090 | 12 | 120 | 90 |
| AB9G12150090 | 12 | 150 | 90 |
| AB9G14060090 | 14 | 60 | 90 |
| AB9G14080090 | 14 | 80 | 90 |
| AB9G14100090 | 14 | 100 | 90 |
| AB9G14120090 | 14 | 120 | 90 |
| AB9G14150090 | 14 | 150 | 90 |
| AB9G16060090 | 16 | 60 | 90 |
| AB9G16080090 | 16 | 80 | 90 |
| AB9G16100090 | 16 | 100 | 90 |
| AB9G16120090 | 16 | 120 | 90 |
| AB9G16150090 | 16 | 150 | 90 |
| AB9G18060090 | 18 | 60 | 90 |
| AB9G18080090 | 18 | 80 | 90 |
| AB9G18100090 | 18 | 100 | 90 |
| AB9G18120090 | 18 | 120 | 90 |
| AB9G18150090 | 18 | 150 | 90 |
| AB9G20060090 | 20 | 60 | 90 |
| AB9G20080090 | 20 | 80 | 90 |
| AB9G20100090 | 20 | 100 | 90 |
| AB9G20120090 | 20 | 120 | 90 |
| AB9G20150090 | 20 | 150 | 90 |

The Abre system is investigational in the US and will be labeled as such. The label will be provided separate from this CIP. Outside the US, the Abre system is CE marked and is labeled as such. Labeling will be provided in local language for CE marked devices. The CE marked devices will be used within intended use as described in the approved IFU for which CE mark has been obtained. In countries where no market release is obtained, the use of the Abre system is limited to the clinical investigation and according the Clinical Investigation Plan. Instructions for Use are available separate from this CIP. The device classification of the Abre system is listed in **Table 4**.

**Table 4: Device Classification**

| Device | Classification by Geography | |
|---|---|---|
| | USA (FDA) | European Union (MDD) |
| Abre system | Class III | Class IIb |

## 8.2 Manufacturer

The Abre self-expanding venous stent system will be manufactured in accordance with standard procedures and specifications under 21 CFR 820 and ISO13485. The manufacturer is listed below:

Medtronic Inc.
710 Medtronic Parkway
Minneapolis, Minnesota 55432
USA

## 8.3 Packaging

The Abre system is delivered in a sterile package for single use only. The label is provided separate from this CIP.

## 8.4 Intended Population

The Abre system is intended for use in the iliofemoral veins for the treatment of symptomatic venous outflow obstruction.

The Abre stent must not be used in patients in whom anticoagulant or antiplatelet therapy is contraindicated and with known hypersensitivity to nickel titanium (nitinol).

## 8.5 Equipment

Any test equipment critical to be used for assessing endpoints (e.g., Duplex Ultrasound, X-ray, IVUS, venography) will be maintained/calibrated according to the site's standard protocol. Maintenance and calibration reports will be monitored periodically.

## 8.6 Product Training Requirements

The implanting investigator will be evaluated to ensure that he/she is qualified by training, education, and experience to implant iliofemoral venous stents. Each implanting investigator must meet the predefined minimum requirement of having performed at least 10 iliofemoral venous stent cases in the year prior to site activation. It is also required that the study site has performed at least 20 venous stenting cases in the year preceding site activation.

The implanting investigator will be trained on the Abre system including, but not limited to at least the following:

- Instructions for Use of the Abre system
- Bench top model of the Abre system including deployment of at least one stent

No roll-in patients are planned for this study.

Additional training requirements are included in the ABRE Study Training Plan.

## 8.7 Product Receipt and Tracking

All sites will be trained on device accountability, including the return of open or unopened devices (for defect, damage, malfunction, expired inventory).

The PI is responsible for maintaining adequate records of the receipt and disposition of all Abre systems as per the Device Accountability Instructions provided in the Investigator Site File.

All sites are required to maintain (investigational) device records that contain the following information on all components shipped to the site for the study:

- (Investigational) device name
- Device model number
- Device lot number
- Date of receipt of device
- Name of person receiving the device
- Name of person using/opening the device (if applicable)
- Date of implant or use (if applicable)
- Subject Identification Number (SID) of subject receiving or using the device (if applicable)
- Disposition (implanted, disposed of, or returned to Medtronic)

For devices that are returned to Medtronic or disposed of, sites are required to document the following additional information:

- The reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date shipped to Medtronic, if returned
- If device is disposed of, the method of disposal

## 8.8 Product Storage

Where investigational, the sites must store devices as labeled and placed in a secure area away from sunlight that is accessible and controlled only by the assigned, trained study personnel at the site.

Where market-released, the site must store devices as labeled.

## 8.9 Product Return

In the event of a device malfunction of the Abre system prior to, during, or after implant (due to conversion to surgery during the index procedure, stent infection, integrity issues triggering explant or identification during autopsy), the device should be returned to Medtronic. Sites should contact their Medtronic clinical study representative to obtain further instruction on device return procedures. All explanted devices will be analyzed by Medtronic. At the end of the study enrollment period, all remaining investigational devices (in US) must be returned to Medtronic.

# 9 Selection of Subjects

## 9.1 Study Population

Patients between 18 and 80 years (inclusive) requiring treatment of a non-malignant venous obstruction within the common iliac, external iliac, and/or common femoral vein may be considered for this study if they meet all of the inclusion and exclusion criteria (I/E criteria).

## 9.2 Subject Enrollment (Point of Enrollment and Inclusion)

The point of enrollment is the time at which the subject signs and dates the informed consent form.

The point of inclusion is the time at which the subject who signed and dated the informed consent form, adhered to all I/E criteria and where the Abre system enters the vasculature.

## 9.3 Subject Screening

Patients identified with symptomatic venous outflow obstruction in the iliofemoral veins requiring a venous stent will be screened by the site's investigative team for possible inclusion in the study.

During the course of the study, Medtronic may limit enrollments to specific indications (i.e. acute DVT, postthrombotic syndrome (PTS), or nonthrombotic iliac vein lesion (NIVL)), if needed in order to achieve a distribution that is similar to the literature review used to develop the study performance goals. Investigators will be notified of specific indications that will no longer be considered for enrollment. This determination will be made during the screening process, at which time the subject would become a screening failure.

**Enrolled**

Patients who meet all general screening criteria will be asked to participate in the study. If the patient agrees to participate, prior to any study-specific tests or procedures, a personally signed and dated informed consent will be obtained. Signing and dating the informed consent form is considered the point of enrollment. Once informed consent has been obtained study-specific tests will be performed to assess any remaining I/E criteria.

**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. The pre-procedure/pre-stenting imaging must be submitted to the core laboratory.

The subject's medical record must indicate that the subject is enrolled in the ABRE Study. Sites will maintain a Subject Identification and Enrollment Log.

These subject categories are described in **Table 5.**

**Table 5: Description of subject categories**

| Subject category | Description |
|---|---|
| Enrolled | Subjects who signed and dated the informed consent form.<br><br>These subjects will be recorded on the Subject Identification & Enrollment Log. |
| Enrolled - not included | Subjects who signed and dated the informed consent form and where the Abre system did not enter the vasculature. For example due to not fulfilling all I/E criteria which could only be assessed after the point of enrollment.<br><br>These subjects will be recorded on the Subject Identification & Enrollment Log. |
| Included | Subjects, who signed and dated the informed consent form, adhere to all I/E criteria and where the Abre system entered the vasculature.<br><br>These subjects will be recorded on the Subject Identification & Enrollment Log. |
| Included - not implanted | Subjects, who signed and dated the informed consent form, adhere to all I/E criteria and where the Abre system entered the vasculature and the Abre stent was not implanted.<br><br>These subjects will be recorded on the Subject Identification & Enrollment Log. |

Failure to obtain a handwritten signed and hand-dated informed consent prior to any study-specific procedures constitutes a deviation, which is reportable to the Institutional Review Board (IRB)/Ethics Committee (EC) (henceforth referred to as ”Ethics Board”), the FDA, and other regulatory authorities as applicable. However, if any required baseline exams (e.g. IVUS, venography, Duplex Ultrasound, blood labs) have been performed as standard of care prior to consenting the patient, they can be used as the baseline/qualifying exams (and will not be considered a deviation), provided they meet the following criteria:

- the investigator determines that the exams contain the protocol-required data and are adequate for evaluation;
- the exams were completed within 30 days prior to the scheduled implant procedure.

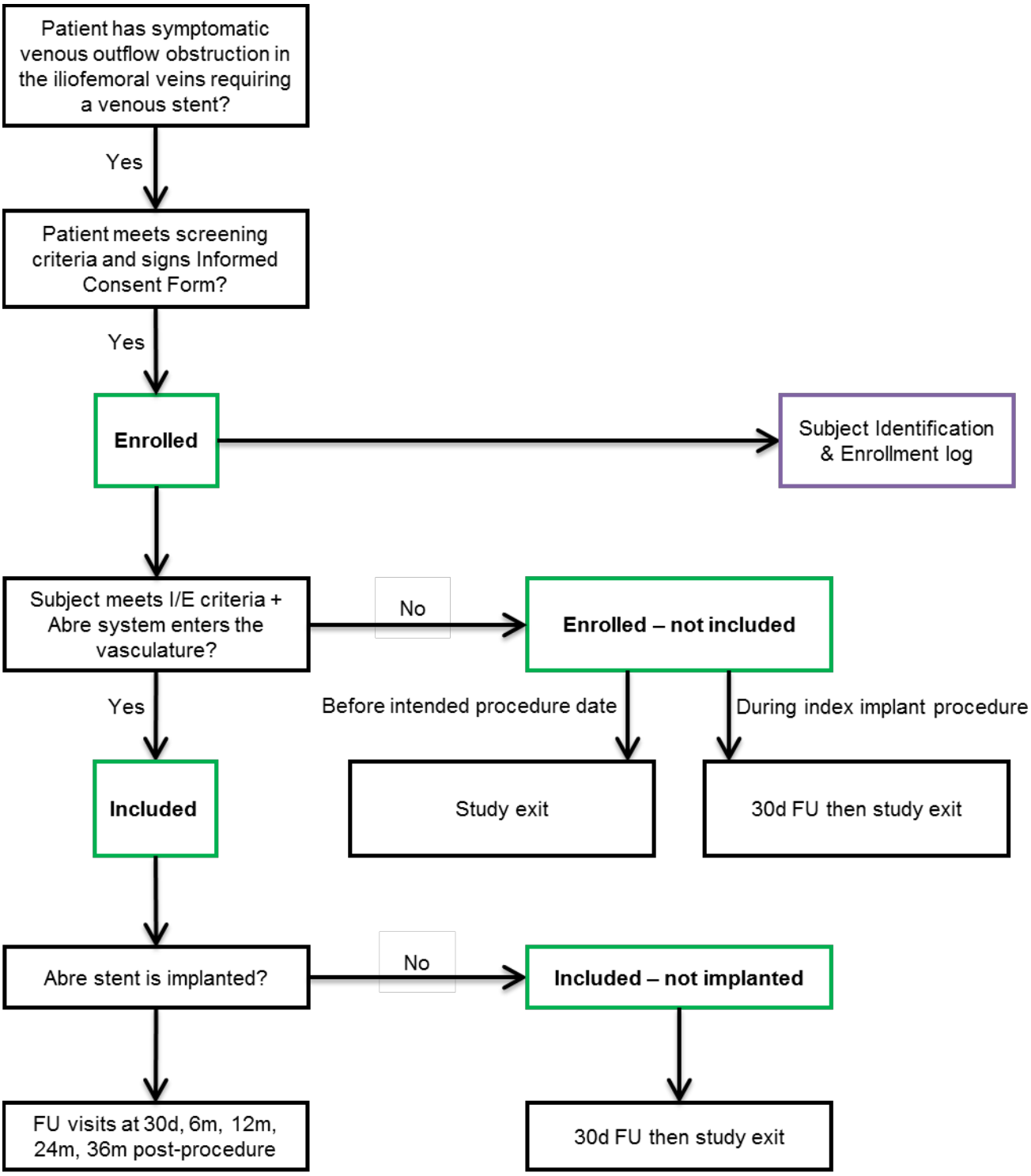



**Figure 4: Flow-Diagram from Subject Screening to Follow-up**

## 9.4 Inclusion Criteria

**General 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 [6]
    b. Venous Clinical Severity Score pain score (VCSS) ≥2 (1)
    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.

**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.

[6] 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.

## 9.5 Exclusion Criteria

**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).

# 10 Study Procedures

## 10.1 Schedule of Events

The clinical study will require follow-up visits at hospital discharge, 30 days, 6-, 12-, 24-, and 36-months post index procedure. **Table 6** and **Table 7** show a detailed overview of the schedule of clinic evaluations and follow-up visits.

**Table 6: Schedule of Assessments and Visit Windows**

| Data Collection Requirement | Screening/Baseline (<30 days before procedure unless otherwise specified) | Procedure | Hospital Discharge | 30 Day (-7/+14 days) | 6 Months (± 30 days) | 12 Months (± 30 days) | 24 & 36 Months (± 30 days) | Unscheduled visit for intervention in target vein |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Demographics, Medical History & Physical Examination | X | | | | | | | |
| Pregnancy Test[1] | X | | | | | | | |
| CEAP Classification | X | | | | | | | |
| Physical Assessment of Limbs | X | | X | X | X | X | X | X |
| Villalta Score, VCSS | X | | | X | X | X | X | X[4] |
| VEINES-QOL/Sym, EQ-5D QOL | X | | | | X | X | X | X[4] |
| Procedure Data | | X | | | | | | X |
| Serum Creatinine, CBC | X | | | | | | | |
| INR (if on warfarin) | X | | | X | X | X | X | X |
| Document Adverse Events | X[2] | X | X | X | X | X | X | X |
| Document Device Deficiencies | | X | X | X | X | X | X | X |
| Medication[3] | X | X | X | X | X | X | X | X |
| Discontinuation Information[5] | | | X | X | X | X | X | X |

[1] Pregnancy test for women of child-bearing potential only. Must be done within 7 days prior to the index procedure.
[2] Adverse Event assessment need to be done as of the moment the subject is enrolled in the study (i.e. subject signed and dated the informed consent form).
[3] Medication which will be collected: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins
[4] Assessments and questionnaires should be taken before any intervention.
[5] The discontinuation data is needed whenever the subject ends involvement in the study.

**Note:** Only approved devices and therapies may be used during the entire study duration.

**Table 7: Schedule of Imaging Assessments and Visit Window**

| Data Collection Requirement | Screening/Baseline (<30 days) | Procedure | | Hospital Discharge | 30 Day (-7 days, +14 days) | 6 Months (± 30 days) | 12 Months (± 30 days) | 24 & 36 Months (± 30 days) | Unscheduled visit for intervention in target vein |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-stenting | Post-stenting | | | | | | |
| Duplex Ultrasound | X | | | X[2] | X | X | X[4] | X | X |
| Venogram | 1 | X[1] | X | | | | 4 | | X |
| IVUS | 1 | X[1] | X | | | | | | X |
| X-ray | | | | | 3 | | X | X | X[5] |

[1] Diagnosis can be made during the screening/baseline prior to the index procedure based on objective imaging using venography or IVUS. Diagnosis can also be made during the index procedure, prior to stenting. In case venogram and IVUS are not performed pre-stenting at the time of the index procedure, the pre-procedure venogram and IVUS should be sent to the core laboratory.
If both screening and pre-procedure venogram/IVUS are performed, then the pre-procedure venogram/IVUS should be sent to the core laboratory.

[2] The DUS examination immediately after the index procedure needs to be performed between 0 and 7 calendar days from the index procedure. When the first examination after the procedure is non-diagnostic, a second examination has to be performed as soon as possible. Every effort should be made to perform this within 7 calendar days after the index procedure.

[3] X-rays at 30 days will be performed on the first 30 subjects only. They will be assessed for first safety analysis (i.e. stent fracture).

[4] 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 subject is obese (e.g. with a BMI >40), or;
(3) is clinically required, or in other words when the subject is having symptoms of venous disease in the target limb requiring a venogram.

[5] Plain x-ray is required pre and post re-intervention to assess for stent fracture.

All imaging examinations as defined in **Table 7** should be performed according to the core laboratory guidelines and will be analyzed by respective independent core laboratories. Exceptionally, the Screening/Baseline Duplex Ultrasound (both limbs) will be performed according to standard of care and will not be sent to the core laboratory.

## 10.2 Subject Consent

### 10.2.1 Consent Materials

Geography-specific templates of the Patient Information and Informed Consent Form (PI/ICF) will be available separate from this CIP. These templates may be modified to suit the requirements of the individual site. For US sites, this must include Health Insurance Portability and Accountability Act (HIPAA) Authorization language. This language may be incorporated into the ICF or (if required by the Ethics Board) included as a separate document.

Medtronic, Ethics Boards, and Competent Authorities (CA), where applicable, shall approve all informed consent documents prior to implementation in the study. Medtronic, Ethics Boards, and CAs, where applicable must pre-approve all language changes to the PI/ICF throughout the course of the study prior to implementation; this includes initial submission, annual reviews (if applicable), and protocol amendment reviews. The original Ethics Board-approved PI/ICF must be retained at the investigational site.

Any revisions required by the Ethics Board must be forwarded to Medtronic for review and approval before the revised consent form is returned to the Ethics Board for final review and full approval.

Medtronic will provide any important new information that impacts the health, safety or welfare of study subjects, for inclusion in PI/ICF updates as it becomes available. Sites should following any Medtronic, CA, or Ethics Board requirements for disseminating new information and re-consenting subjects during the course of the study.

### 10.2.2 Informed Consent Process

The investigator (or authorized designee) must administer the approved PI/ICF to each prospective study patient without coercion or undue improper influence on, or inducement of, the patient to participate. During the consent discussion the investigator (or authorized designee) must fully inform the patient of all pertinent aspects of the study, using native non-technical language that is understandable to the patient. The patient must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled, and also informed that withdrawal from the study will not jeopardize their future medical care. The patient must also be informed that by participating in the study, they are not waiving their legal rights. The patient must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the patient. All items discussed in the PI/ICF must be explained.

Informed consent will be obtained in writing from the patient. The date of consent and process by which the consent was obtained (including documentation of special circumstances, if applicable) will be documented in the patient's medical record prior to any study-specific procedures. Patient informed consent must be obtained in accordance with the national and local laws, regulations and guidelines of each site. The institutional standard procedure consent form does not replace the study PI/ICF.

The subject's signature and date of consent serve to document that they understand the written and verbal information that the investigator (or authorized designee) provides, and their agreement to participate and collect their medical data. The investigator (or authorized designee) who conducted the informed consent process must provide their handwritten signature and date the consent was completed on the ICF. The ICF must be signed and dated prior to any specific protocol assessments or procedures.

However, if any required baseline exams (e.g. IVUS, venography, Duplex Ultrasound, blood labs) have been performed as standard of care prior to consenting the subject, they can be used as the baseline/qualifying exams (and will not be considered a deviation), provided they meet the following criteria:

- the investigator determines that the exams contain the protocol-required data and are adequate for evaluation;
- the exams were completed within 30 days prior to the scheduled implant procedure.

The original signed and dated ICF will be kept at the investigational site. A copy of the signed and dated ICF will be provided to the subject.

### 10.2.3 Special Circumstances for Informed Consent Process and Signature

If a patient cannot read or write, an impartial witness must be present during the entire informed consent discussion. The written PI/ICF (and any other information) shall be read aloud and explained to the patient and witness. The witness will sign and personally date the ICF attesting that the information was accurately explained and that consent was freely given. The patient will sign and date if possible.

Given the investigational status of the Abre system in the US, and the availability of approved endovenous stents in some geographies, emergency cases are not allowed under this protocol.

Given the commercial availability of other endovenous stents in some geographies, requests for compassionate use of the Abre stent are not anticipated.

## 10.3 Screening/Baseline Procedures (-30 days)

The following baseline evaluations will be completed and recorded on the appropriate eCRF. Baseline evaluations are to be completed within 30 days of the scheduled implant procedure unless otherwise specified.

- Informed consent
- Demographics
- Medical history
- Physical examination
- Pregnancy test for women of child bearing potential only. This must be done within 7 days prior to the index procedure.
- CEAP classification (for both limbs)
- Physical assessment of limbs
- Villalta score, VCSS (for both limbs)
- Quality of life questionnaires: EQ-5D and VEINES-QOL/Sym
- Blood tests (See **Section** 10.3.2 Blood Tests)
- INR required for subjects on warfarin
- Venogram or IVUS for diagnosis if performed as standard of care. This diagnosis can also be made during the index procedure, prior to stenting.
- Duplex ultrasound (DUS) (both limbs)
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers

- Adverse event assessment need to be done as of the moment the subject is enrolled in the study (i.e. subject signed and dated the informed consent form).

### 10.3.1 Demographics, Medical History & Physical Examination

A careful medical history and physical examination should be taken prior to the implant procedure. For any interventions, the date of the most recent intervention should be captured.

Data to be collected at baseline:

- Gender
- Age at time of enrollment
- Race/Ethnicity, to be collected per the FDA Guidance for Collection of Race and Ethnicity Data in Clinical Trials (2016) [38], in support of regulatory submissions in the US (FDA).
- Risk factors, such as hypertension, diabetes, hyperlipidemia, tobacco use, obesity (BMI), previous knee/hip replacement, immobility and any other cardiovascular risk factors, with measure of severity and current treatment
- Co-existing cardiovascular conditions (including, but not limited to superficial ablation, congestive heart failure, peripheral vascular disease, previous myocardial infarction (MI))
- Symptoms
- Physical examination
- Assessment of target lesion and access vessel characteristics
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins;

### 10.3.2 Blood Tests

The following blood tests are required:

- Serum creatinine for GFR calculation (GFR must be ≥30 to be included in the study). Any method to perform the GFR calculation is allowed;
- White Blood Cell (WBC) count (must be ≥3,000 cells/$mm^3$ and ≤ 12,500 cells/$mm^3$ to be included in the study)
- Platelet count (must be ≥ 50,000 cells/$mm^3$ and ≤1,000,000 cells/$mm^3$ to be included in the study);
- Hemoglobin;
- Hematocrit;
- INR required for subjects on warfarin.

## 10.4 Acute DVT Subjects

Acute DVT subjects must be treated with the Abre stent within 14 days after onset of symptoms. Subjects with acute deep vein thrombosis (DVT) must first undergo successful treatment of acute thrombus. This must be done within 14 days after the onset of symptoms and only with market released devices. Successful treatment is defined as less than 30% residual thrombus by venogram, as determined by physician, and no bleeding, no symptomatic pulmonary embolism (confirmed by imaging), and no renal compromise. Subjects with underlying obstructive lesions may be included in the study within the same procedure, or the procedure may be staged.

## 10.5 Implant Procedure

Detailed information on intended use of the device, indications, and contraindications, as well as a complete list of warnings, precautions, and potential adverse events, are included in the IFU. The IFU will be provided with each device.

### 10.5.1 Procedure Data

The following data shall be recorded for each subject in the study:

- Date of procedure
- Indication for stenting: acute DVT, NIVL, PTS, and any combination of these
- Identification data for the stent(s)
- Details of procedure, including any adjunctive vascular procedure performed
- Chosen access sites
- Medications: Antithrombotics, Thrombolytics
- Assessment of handling, visualization, deployment, and withdrawal
- Assessment of patency, positioning, and integrity of the stent
- Adverse events
- Comparison of intended and actual stent location
- Date of hospital discharge

### 10.5.2 Imaging

During the index procedure, venography and IVUS is required, prior and post stent placement to aid with stent sizing and lesion assessment.

### 10.5.3 IVC Filter Placement

Inferior Vena Cava (IVC) filter placement is at the discretion of the physician. IVC filter placement is not encouraged, however should be considered in the following situations:

- presence of floating thrombus in iliocaval segments;
- planned use of mechanical thrombectomy in the presence of acute thrombus.

IVC filter should be removed as soon as deemed safe by the operating physician.

### 10.5.4 Inflow Requirements

Negative outcomes are best avoided by good inflow directed by IVUS in the least diseased portion of the vein above the deep femoral vein. Good inflow involves either the femoral or deep femoral vein inflow being patent and at least a caudal section of the common femoral vein that is free of significant disease. Good inflow will be determined by the investigator.

### 10.5.5 Lesion(s)

The target lesion is defined as 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. When stented, the complete stented area is considered 'lesion' and should be treated as such during follow-up assessments.

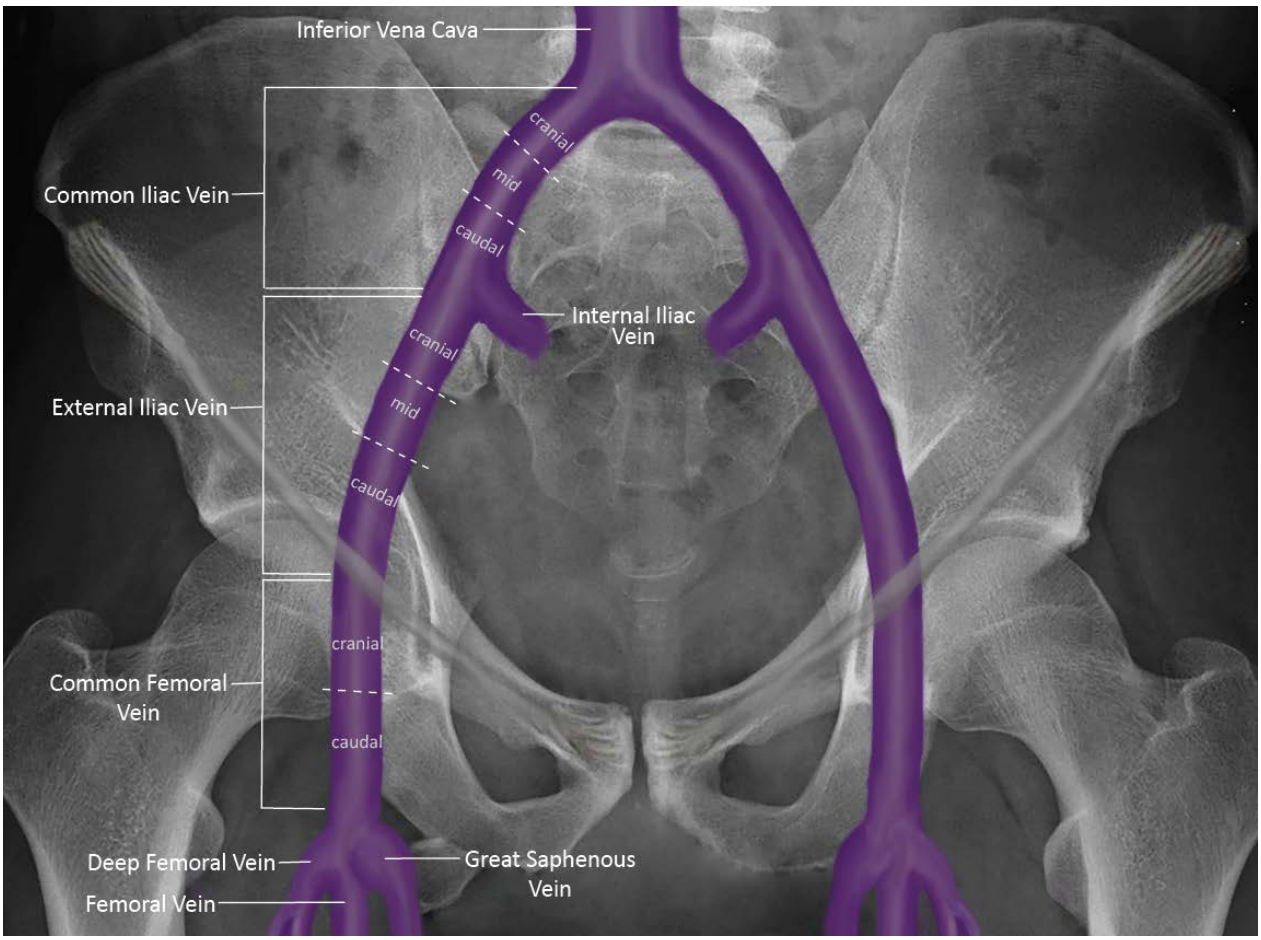



**Figure 5. Venous anatomy**

### 10.5.6 Predilation

Access site should be at the discretion of the physician, however it is strongly recommended not to use the ipsilateral common femoral vein and access from the ankle.

Predilation of the lesion with a balloon catheter is required to be the same diameter of the stent to be implanted, i.e. if a 14 mm stent is to be implanted, a 14 mm diameter balloon must be used. A high pressure balloon is highly recommended.

At a minimum the balloon should be inflated up to nominal pressure and should be inflated within the segment that it is intended to be stented. Remove the balloon from the subject while maintaining access with the guidewire.

### 10.5.7 Stent Size Selection

To optimize visualizing of the true extent of a venous lesion, venogram and IVUS can be used. However, IVUS is the preferred modality.

**Stent length**

It is important that the proximal and distal ends of the stents lie in a relatively normal/healthy venous segment. Therefore, a stent length must be chosen that extends cranial and caudal to the target lesion, covering at minimum 1 cm cranial and 1 cm caudal, if the disease allows. Additional coverage can reduce the risk of restenosis. The Abre stent should not occlude the inflow of the contralateral limb or touch the contralateral wall.

**Stent diameter**

Vein diameters can be measured using one of the following two methods:

1. Using IVUS: take the average of the minimum and maximum diameters of a normal segment of vein in the same anatomical segment;
2. Using Venogram: take the average diameter of a normal segment of vein in the same anatomical segment in two planes.

Considering the estimated anatomic vessel diameter, the appropriate Abre stent diameter must be selected. A stent with a diameter of at least 2 mm more than the chosen reference vessel diameter is recommended to achieve good wall apposition.

Reference vessel diameter can be obtained by one of the following methods:

1. Measure the diameter of a normal segment of an appropriate segment of the target vein (which generally should be the most caudal segment);
2. Measure the diameter of the vein in an appropriate segment of the contralateral limb;
3. Use the literature reference vessel diameter for the appropriate segment:
    a. Common Iliac Vein: 16 mm
    b. External Iliac Vein: 14 mm
    c. Common Femoral Vein: 12 mm

Proper size selection reduces stent migration and ensures appropriate stent apposition to the vessel wall.

### 10.5.8 Stent Placement

The Abre delivery system should be advanced until the leading edge of the stent is beyond the target lesion. Whenever possible, one stent should be used to cover the entire length of the target lesion.

**Multiple stents**
If multiple stents are needed to cover the entire length of the target lesion, they should be implanted in an overlapping manner with a minimum overlap of 1.5 cm. The more cranial stent should be placed first. It is recommended to use the same stent diameter. If different diameters are needed, the smaller diameter stent should be placed first. Non-stented areas in between stents, i.e. skip areas, are not allowed. Stents ending in the inguinal ligament must be avoided.

### 10.5.9 Post-dilation

Post-dilation of the lesion with a balloon catheter is recommended up to the diameter of the implanted stent to achieve the expected nominal stent diameter.

## 10.6 Hospital Discharge

The discharge visit will occur at the time of subject's discharge from the hospital. The following evaluations will be completed and data recorded on the Discharge eCRF:

- Duplex ultrasound (target limb). The DUS examination immediately after the index procedure needs to be performed between 0 and 7 calendar days from the index procedure. When the first examination after the procedure is non-diagnostic, a second exam has to be performed as soon as possible. Every effort should be made to perform this within 7 calendar days after the index procedure;
- Duplex ultrasound (contralateral limb); image of the CFV waveform only.
- Physical assessment of limbs;
- Adverse events/device deficiency;
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins;
- Compression stockings. Subjects will be instructed to wear medical grade (≥ 20 mm Hg) compression stockings (above or below knee) as instructed by their physician with compliance encouraged. The use of compression stockings will be evaluated via the VCSS;
- Discontinuation information (in case the subject ends involvement in the study).

## 10.7 30 Day (-7/+14 days) Post-Procedure Follow-Up Assessment

Subjects will be seen in the office at 30 days (23-44 days) post-procedure. The following evaluations will be completed and data recorded on the Follow-up eCRF:

- Physical assessment of limbs;
- Villalta Score and VCSS (both limbs);
- INR for subjects on warfarin;
- Duplex Ultrasound (target limb);
- Duplex ultrasound (contralateral limb); image of the CFV waveform only.
- X-ray (target limb); only on the first 30 subjects in the study for first safety analysis (i.e. stent fracture). Sites will be notified if this is no longer needed;

- Adverse events/device deficiency;
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins;
- Discontinuation information (in case the subject ends involvement in the study).

## 10.8 6 Months (± 30 days) Post-Procedure Follow-Up Assessment

Subjects will be seen in the office at 6 months (150-210 days) post-procedure. The following evaluations will be completed and data recorded on the Follow-up eCRF:

- Physical assessment of limbs;
- Villalta Score and VCSS (both limbs);
- Quality of Life Questionnaires: EQ-5D and VEINES-QOL/Sym;
- INR for subjects on warfarin;
- Duplex Ultrasound (target limb);
- Duplex ultrasound (contralateral limb); image of the CFV waveform only.
- Adverse events/device deficiency;
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins;
- Discontinuation information (in case the subject ends involvement in the study).

## 10.9 12 Months (± 30 days) Post-Procedure Follow-Up Assessment

Subjects will be seen in the office at 12 months (330-390 days) post-procedure. The following evaluations will be completed and data recorded on the Follow-up eCRF:

- Physical assessment of limbs;
- Villalta Score and VCSS (both limbs);
- Quality of Life Questionnaires: EQ-5D and VEINES-QOL/Sym;
- INR for subjects on warfarin;
- Duplex Ultrasound (target limb);
- Duplex ultrasound (contralateral limb); image of the CFV waveform only.
- Venogram (target limb), when required.
    - An additional venogram must be performed when:
      (1) DUS assessment is suggestive of ≥50% restenosis or occlusion per investigator assessment;
      (2) when DUS is non-diagnostic or suboptimal such as when a subject is obese (e.g. with a BMI >40), or;
      (3) is clinically required, or in other words when the subject is having symptoms of venous disease in the target limb requiring a venogram.
- X-ray (target limb);
- Adverse events/device deficiency;
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins;
- Discontinuation information (in case the subject ends involvement in the study).

## 10.10 24 and 36 Months (± 30 days) Post-Procedure Follow-Up Assessment

Subjects will be seen in the office at 24 months (690-750 days) and 36 months (1050-1110 days) post-procedure. The following evaluations will be completed and data recorded on the Follow-up eCRF:

- Physical assessment of limbs;
- Villalta Score and VCSS (both limbs);
- Quality of Life Questionnaires: EQ-5D and VEINES-QOL/Sym;
- INR for subjects on warfarin;
- Duplex Ultrasound (target limb);
- Duplex ultrasound (contralateral limb); image of the CFV waveform only.
- X-ray (target limb);
- Adverse events/device deficiency;
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins;
- Discontinuation information (in case the subject ends involvement in the study).

## 10.11 Unscheduled Visits

Unscheduled visits are additional non-scheduled visits that occur at times other than the predetermined intervals and during which an intervention in the target vein takes place. If the Abre stent(s) is(are) explanted, the subject will be followed for safety reporting only for 30 days post-explant. AE data should be collected on the AE eCRF, and study exit data should be collected on the Study Exit eCRF. It is not allowed to implant a new Abre stent during the reintervention. The following assessments will be completed and the data will be recorded on the Follow-up eCRF:

- Physical assessment of limbs
- Villalta Score and VCSS (for both limbs, should be taken before any intervention)
- Quality of Life Questionnaires: EQ-5D and VEINES-QOL/Sym (should be taken before any intervention)
- INR for subjects on warfarin
- Duplex ultrasound (target limb)
- Duplex ultrasound (contralateral limb); image of the CFV waveform only.
- Venogram (target limb)
- IVUS (target limb)
- Plain X-ray (target limb) is required pre and post re-intervention to assess for stent fracture
- Secondary procedure data
- Adverse events/device deficiency
- Medications: Antithrombotics, Antibiotics, Immunosuppressants, NSAIDs, Steroids, Diuretics, Calcium-channel blockers, Statins
- Discontinuation information (in case the subject ends involvement in the study)

## 10.12 Assessments

### 10.12.1 Antithrombotics

The following anticoagulation and antiplatelet treatment is ***recommended*** pre-, peri-, and post-stenting procedure.

**Pre-procedure**

If subject is taking an anticoagulant, this needs to be stopped prior to intervention with an appropriate transition regime.

If subject is on warfarin, a slight increase in the pre-procedure prothrombin time (INR ≤ 1.7) is not a contraindication to proceed with the procedure.

**Peri-procedure**

In all subjects, full anticoagulation is instituted prior to the index procedure and it is important to maintain adequate treatment throughout the procedure. The regimen is to be determined by the investigator.

A suggested anticoagulation regimen for chronic subjects is:

- a heparin bolus of 5000 units, after placement of the sheath in the access vessel;
- followed by bolus of 5000 units or infusion of 100 U/kg to keep ACT>200 seconds for a full systemic anticoagulation.

**Post-procedure**

Full anticoagulation should be commenced within 4 hours of completion of the procedure. Anticoagulation should follow local guidance. However, when using warfarin, an INR>2.0 with appropriate bridging cover is recommended. DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) can be used instead of warfarin.

**Duration**

The following minimum anticoagulation treatment time is recommended:

- 6 months in non-thrombotic subjects;
- 12 months in thrombotic subjects;
- long-term treatment for subjects with thrombophilia.

**Antiplatelets**

With respect to antiplatelet treatment, the following recommendations are provided:

- A regimen of dual antiplatelet treatment in addition to anticoagulation should be carefully considered in light of the high bleeding risk. If used, dual antiplatelet treatment in addition to anticoagulation should be limited to only the first 6 weeks following the index procedure.
- After discontinuation of anticoagulation therapy, consider switching subjects to an antiplatelet therapy (if not currently ongoing);

## 10.12.2 CEAP Classification

At baseline, the American Venous Forum CEAP classification (2004) will be used to provide a comprehensive objective classification of the severity of the veins. This assessment must be performed for both limbs. The CEAP Classification needs to be assessed by a medical doctor or qualified delegated person. See Appendix C CEAP Classification.

## 10.12.3 Scores

### 10.12.3.1 Villalta Score

The Villalta score will categorize the severity of postthrombotic syndrome (PTS). The Villalta score should be assessed for all subjects for both limbs at baseline, 30-days, 6-, 12-, 24-, 36-Month and Unscheduled follow-up visits. At Unscheduled visits, the Villalta should be taken before an intervention in the target vein takes place. The Villalta Score needs to be assessed by a medical doctor or qualified delegated person. See Appendix D Villalta Score.

### 10.12.3.2 Venous Clinical Severity Score (VCSS)

The VCSS will be used to assess changes in disease severity over time. The VCSS should be assessed for both limbs at baseline, 30-days, 6-, 12-, 24-, 36-Month and Unscheduled follow-up visits. At Unscheduled visits, the VCSS should be taken before an intervention in the target vein takes place. The VCSS needs to be assessed by a medical doctor or qualified delegated person. See Appendix E Venous Clinical Severity Score (VCSS).

## 10.12.4 Quality of Life questionnaires

Health-related quality of life outcomes will be assessed at baseline and 6-, 12-, 24-, 36-Month follow-up visits using the EQ-5D and VEINES-QOL/Sym questionnaires. See Appendix F EQ-5D and Appendix G VEINES-QOL/Sym questionnaire. These questionnaires need to be completed either by the subject or by a delegated person who asks the questions to the subject and completes the questionnaire on behalf of the subject. In case it is needed a proxy EQ-5D questionnaire might be used.

## 10.12.5 Pregnancy Test

For female subjects of child-bearing potential, a (urine or blood) pregnancy test will be done at baseline (within 7 days prior to the index procedure) to confirm that the subject is not pregnant. Subjects exempt from this requirement are those who have been surgically sterilized, who are infertile, or who have been post-menopausal for at least 12 months (no menses).

## 10.12.6 Imaging

### 10.12.6.1 Venogram

A venogram (target limb) **must** be performed:

- during the index procedure, prior and post stent placement to aid with stent sizing and lesion assessment;
- in case a re-intervention in the target vein takes place;
- to assess the primary effectiveness performance goal endpoint during the 12 month follow-up visit only when:

  (1) DUS assessment is suggestive of ≥50% restenosis or occlusion per investigator assessment,

  (2) when DUS is non-diagnostic or suboptimal such as when a subject is obese (e.g. with a BMI>40), or

  (3) clinically required, or in other words when the subject is having symptoms of venous disease in the target limb requiring a venogram.

Furthermore, a venogram (target limb) **may** be performed:

- during screening: the diagnosis can be made based on objective imaging using venography or IVUS;
- at all other time points, an additional venogram may be performed at the investigator discretion.

In case that the subject refuses a venogram, it will be documented in the eCRF. This is not considered a deviation.

All venographic imaging examinations should be performed according to the core laboratory guidelines and will be analyzed by an independent core laboratory (See **Section 13.4**).

### 10.12.6.2 Duplex Ultrasound (DUS)

The screening DUS should be performed per standard of care in both limbs. All DUS after the index procedure should be performed in the target limb, including an image of the contralateral CFV waveform.

The DUS exam immediately after the index procedure needs to be performed between 0 and 7 calendar days from the index procedure. When the first exam after the procedure is non-diagnostic, a second exam has to be performed as soon as possible. Every effort should be made to perform this within 7 calendar days after the index procedure.DUS will be performed to assess patency during the 6, 12, 24, 36 months follow-up visits.

All DUS examinations, except the screening DUS, should be performed according to the core laboratory guidelines and will be analyzed by an independent core laboratory (See **Section 13.3**).

#### 10.12.6.3 Intravascular ultrasound (IVUS)

During the following timepoints, IVUS (target limb) is required:

- during the index procedure, IVUS is required, prior and post stent placement to aid with stent sizing and lesion assessment;
- during unscheduled follow-up visits, if the subject returns to the hospital at times other than the predetermined intervals and during which an intervention in the target vein takes place, prior and post intervention.

Furthermore, an IVUS (or venography) may be performed during the screening for diagnostic purposes.

All IVUS examinations should be performed according to the core laboratory guidelines and will be analyzed by an independent core laboratory (See **Section 13.4**).

#### 10.12.6.4 X-ray

During the following timepoints an X-ray (target limb) is required to assess stent fracture:

- at 30-days for first safety analysis for the first 30 subjects;
- at 12, 24, and 36 months for all subjects;
- during reinterventions (unscheduled visits) pre- and post- reintervention.

All X-ray examinations should be performed according to the core laboratory guidelines and will be analyzed by an independent core laboratory (See **Section 13.4**).

### 10.12.7 Physical Assessment of Limbs

Physical assessment of both limbs should be performed at baseline, hospital discharge, 30-days, 6-, 12-, 24- and 36-months follow-up visit and unscheduled visits. The following assessments should be done:

- circumference of the thigh (highest value between hip and knee)
- circumference of the calf (highest value between knee and ankle)
- time of the assessment
- presence of lymphedema

Other physical assessment (e.g. ulcers) are covered by the clinical scores.

These should be performed by principal investigator or delegated persons.

## 10.13 Deviation Handling

A deviation is any event in which the study is not conducted according to the CIP and/or agreement. Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain Ethics Board approval before the start of enrolling subjects in the study
- Included subject did not meet inclusion/exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject did not complete follow-up visit
- Follow-up visit was completed outside window
- Unauthorized use of Abre system(s)
- Adverse events/UADE or device deficiencies not reported in the required timeframe by country regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of subjects during lapse of Ethics Board approval
- Subject inclusion limits exceeded

The investigator is not allowed to deviate from the CIP, except when necessary to protect the life or physical well-being of a subject in an emergency situation. Deviations must be reported to Medtronic on the Deviation eCRF.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Ethics Board as well as Medtronic as soon as possible but no later than five (5) working days from the date of the deviation occurrence.

Reporting of all other deviations should comply with Ethics Board policies, local laws, regulatory agency requirements and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation.

Refer to **Table 16** and **Table 17** for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions which may include amending the CIP, conducting additional training, terminating the investigation, etc. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment at that site until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

## 10.14 Subject Withdrawal or Discontinuation

### 10.14.1 Subject Withdrawal

It is the subject's right to withdraw at any time from the study and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled, and without jeopardizing their future medical care. The investigator may withdraw the subject at any time to protect the health, safety, or welfare of the subject. At the last point of contact (if outside a study-required visit), the subject's vital status should be recorded on a Study Exit eCRF, and every effort should be made to collect the status of any ongoing adverse events prior to withdrawal.

### 10.14.2 Lost-to-Follow-up

The subject may only be considered lost to follow-up after all efforts to obtain compliance are exhausted. At a minimum, four attempts must be made to contact the subject and documented in the subject's records:

- 3 telephone attempts to the subject's last known phone number, and if unsuccessful,
- 1 certified letter from the PI to the subject's last known address

If the site is unable to reach the subject after the documented attempts, the site should make every attempt to verify the subject's vital status (alive or deceased). A Study Exit eCRF should be completed. If the subject returns to the study site thereafter, the Study Exit eCRF can be deleted and follow-up data can be collected. A Deviation eCRF should be completed for the missed visit(s), if appropriate.

### 10.14.3 Subject Discontinuation

All subjects will be encouraged to remain in the study through the last follow-up visit. Included subjects who discontinue participation prematurely will be included in the analysis of results, but will not be replaced in the inclusion of total study subjects. If the subject discontinues participating in the study prior to completing the study requirements, the reason for withdrawal will be recorded in the subject's study records and on the Study Exit eCRF.

There are many scenarios in which a subject may exit the study. **Table 8** details how the data will be handled for each scenario.

### 10.14.4 Medical Care after Study Exit

After study exit, the subjects will be followed as per routine standard of care by the investigational site or a treating physician. Relevant medical records may be made available by the investigational sites for the treating physician per local laws and regulations if needed for further subject treatment. As per local law and regulation, the investigator may be contacted by the treating physician in case of questions related to the study device and treatment.

Sites shall request permission from the subject to follow-up outside of the study, if issues arise with the Abre stent safety or performance.

## 10.15 Recording Data

**Source Documents**

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

In general, eCRFs (or paper copies) may not serve as source documents. An exception is select data on the Product Accountablity Log.. Source documentation for data elements not routinely captured in medical records may vary from site to site; the site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made, and (3) a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

### Data Collection

**Table 8** describes which data will be collected for each scenario and subject category.

**Table 8: Overview data collection for different scenarios**

| Category | Subcategory | | PIC signed | Subject identification & enrollment log | I/E criteria met | Required eCRF's | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Screening | Baseline | Procedure | AE | Device deficiency | Reintervention | FU | Study Exit |
| | | | | | | | | | | | | | |
| Enrolled[1] – not included | Study Exit before intended procedure date | | X | X | | X | | | X[3] | | | | X |
| | Screening failure during implant procedure | | X | X | | X | X | | X[3] | | | | X[4] |
| Included[2] | Not implanted, Abre system entered the vasculature | | X | X | X | X | X | X | X[3,5] | X[3] | | | X[4] |
| | Implanted – 36m FU | | X | X | X | X | X | X | X[3] | X[3] | X[3] | X | X |
| | Implanted – Explanted | | X | X | X | X | X | X | X[3] | X[3] | X | X[5] | X[5] |
| | Implanted – Early study discontinuation | | X | X | X | X | X | X | X[3] | X[3] | X[3] | X[6] | X[6] |

[1] Enrolled: subject who signed and dated the informed consent form.
[2] Included: subject who signed and dated the informed consent form, adhered to all I/E criteria and where the Abre system entered the vasculature.
[3] As applicable.
[4] Subject must be followed for 30 days for safety assessment, then complete Study Exit eCRF. No images need to be sent to the core laboratories if Abre system did NOT enter the vasculature.
[5] After explant, subject must be followed for 30 days for safety assessment, then complete Study Exit eCRF.
[6] Complete all required/unscheduled FU visit eCRFs through last visit completed, then complete Study Exit eCRF.

# 11 Risks and Benefits

## 11.1 Potential Risks

There are risks associated with any endovascular procedure. The risks associated with the Abre system are believed to be similar to those associated with the existing endovascular stent systems in clinical use or commercially available for the treatment of symptomatic iliofemoral venous outflow obstruction. **Table 9** lists all potential adverse events associated with the implantation of the Abre stent.

**Table 9: Potential adverse events**

| | | |
|---|---|---|
| - Access failure<br>- Access site infection<br>- Allergic reaction to contrast medium or procedure medications<br>- Allergic reaction to nitinol or other device materials<br>- Arrhythmia<br>- AV fistula<br>- Bleeding<br>- Bruising<br>- Death<br>- Device breakage<br>- Device maldeployment<br>- Edema | - Fever<br>- Hematoma<br>- Hypotension, nausea, or other vasovagal response<br>- Infection<br>- Myocardial infarction<br>- Pain<br>- Pseudoaneurysm<br>- Pulmonary embolism<br>- Renal insufficiency/renal failure (new or worsening)<br>- Sepsis<br>- Stent fracture<br>- Stent malapposition<br>- Stent malposition | - Stent migration<br>- Stroke/paradoxical embolism/transient ischemic attack/intracerebral hemorrhage<br>- Tissue necrosis<br>- Transfusion reaction following blood transfusion for treatment of major bleeding<br>- Vessel damage, including perforation or rupture<br>- Venous occlusion/thrombosis, within or outside of stented segment |

Additional risks for the subject due to participation in the study may include:

- Discomfort during the imaging scans
- Potential significant radiation exposure due to beam intensity and length of time of imaging, resulting in acute radiation injury as well as increased risk for physical and genetic defects to subjects.

The following measures will be implemented to minimize any risks to study subjects:

- Investigator and study personnel will be trained to the design of the Abre system, its application and preclinical results.
- Eligibility criteria and screening procedures will be followed to ensure that appropriate subjects are enrolled and included.
- Investigator will adhere to the Abre system Instructions For Use packaged with the device.
- The subjects will be carefully monitored throughout the study period.
- The investigator will evaluate the subject adverse events during the course of the study.
- Data submitted from the investigative centers will be monitored during the course of the study.
- Monitoring visits will be conducted to evaluate protocol compliance and data quality.
- Safety and effectiveness data obtained during the course of the study will be shared with investigators in periodic reports to increase understanding of the device and potential adverse events.

- A Data Safety Monitoring Board, Clinical Events Committee, and imaging core laboratory will be established to independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being.
- If a woman is pregnant or becomes pregnant, implantation of the study device may involve risks to the embryo or fetus that are unknown at this time. Therefore, pregnant women will be excluded from the study. If a female subject becomes pregnant during the conduct of this clinical research study they need to inform the investigational site immediately without any unjustified delay. Continuation in the study or withdrawal from the study will be up to the investigator's discretion.

Potential treatments for the foreseeable risks may include medication, surgery, medical monitoring or other applicable treatments, and will be provided at the discretion of the investigator.

Any unanticipated or unforeseen complications will be reported by the principal investigator (or authorized designee) to the Ethics Board and Medtronic. Medtronic is responsible to report any necessary findings to the appropriate regulatory agencies/bodies in each of the respective geographies.

## 11.2 Potential Benefits

### 11.2.1 Potential benefits of the Abre system

Potential benefits from use of the Abre system have not been documented; nevertheless, they are expected to be similar to those associated with venous stent systems currently in clinical trials or commercially available. The primary benefit is the recanalization of iliofemoral stenosis or occlusion with restoration of blood flow. The potential benefits are improvement of limb pain, swelling, skin changes and ulcer healing, and enhancement of quality of life.

The Abre system has several design features that positively impact the performance of the device for its intended use and is expected to offer additional benefits.

These design features are reflected in **Figure 6**.


**Figure 6: Design features Abre stent**

The Abre stent:

- is available in a wide range of sizes in order to provide individually tailored treatment;
- is structurally strong, possessing lateral compression resistance and radial outward force which allow for maintenance of lumen patency in both compressive and non-compressive lesions;
- is flexible to avoid possible stent fracture caused by the extensive kinking which occurs due to placement in the highly mobile groin;
- is durable which may result in reduced likelihood of loss of lumen patency as a result of stent fracture over the lifetime of the stent;
- is accurate in deployment and enables repeatable (consistent) product performance due to minimal stent foreshortening, reduced jumping and enhanced isolation sheath.

### 11.2.2 Potential benefits of the ABRE Study

Subjects enrolled in the study may have additional contact with their physicians or other medical care staff beyond their normal standard of care visits, which may provide benefit from a patient care perspective.

Furthermore, the information obtained during this study will be used scientifically. The results of this study can help physicians understand the safety and effectiveness of the Abre system.

## 11.3 Risk-Benefit Rationale

It has been demonstrated that stent placement for iliofemoral venous outflow obstruction can be performed safely and that these devices are effective in restoring and maintaining iliofemoral vessel patency.

Any potential risks with this study are minimized by selecting qualified investigators, careful assessment of each subject prior to, during, and after implantation. Medtronic has further minimized the possibility of risks by completing product testing prior to the use of the Abre system in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

The investigator in addition performs a continuous monitoring, assessment, and documentation of any risks.

The risks associated with the Abre stent or participation in this study are not anticipated to be worse than the risks normally associated with the use of other commercially available devices.

Risk management for the Abre system is performed in accordance with EN ISO 14971:2012. Furthermore, the indications and contraindications are provided in the Instructions for Use.

# 12 Adverse Event Assessments

## 12.1 Definitions/Classifications

### 12.1.1 Definitions

The definitions to be applied for the purposes of safety reporting are provided in **Table 10**.

**Table 10**: **Definitions**

| Event Type | Definition |
|---|---|
| Adverse Event (AE)<br><br>(EN ISO14155:2011 3.2) | Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.<br><br>*NOTE 1: This definition includes events related to the investigational medical device or the comparator.*<br><br>*NOTE 2: This definition includes events related to the procedures involved.*<br><br>*NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.* |
| Serious Adverse Event (SAE)<br><br>(EN ISO14155:2011 3.37) | Adverse event that<br><br>a) led to death,<br>b) led to a serious deterioration in the health of the subject, resulting in<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, or<br>3) in-patient or prolonged hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) led to foetal distress, foetal death or a congenital abnormality or birth defect.<br><br>*NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* |
| Adverse Device Effect (ADE)<br><br>(EN ISO14155:2011 3.1) | Adverse event related to the use of an investigational medical device.<br><br>*NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.*<br><br>*NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.* |

| Event Type | Definition |
|---|---|
| Serious Adverse Device Effect (SADE)<br><br>(EN ISO14155:2011 3.36) | Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event. |
| Unanticipated Adverse Device Effect (UADE)<br><br>(21 CFR 812.3) | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |
| Unanticipated Serious Adverse Device Effect (USADE)<br><br>(EN ISO14155:2011 3.42) | Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. *NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.* |
| Device Deficiency<br><br>(EN ISO14155<br><br>:2011 3.15) | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.<br><br>*NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.* |

### 12.1.2 Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the study devices and implant procedure will be classified as not related, unlikely, possible, probably, causal relationship.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. Medtronic and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where Medtronic remains uncertain about classifying the adverse event, it should not exclude the relatedness and classify the event as ‘possible related’.

The causal relationships to the Abre system and Abre stent implant procedure are defined in **Table 11**.

**Table 11: Adverse Event Causal Relationship Definitions**

| Related to | Definition |
|---|---|
| Abre system | Any AE involving the function of the device, or the presence of the device in the body. Included in this category are events that are directly attributed to the device. |
| Abre stent implant procedure | Any AE that occurs within 30 days of the Abre stent implant procedure unless specifically shown not to be related to that procedure. |

### 12.1.3 Anticipated Adverse Events

The list of anticipated adverse events and anticipated adverse product effects, including their likely incidence, mitigation and recommended treatment are included in **Table 12**.

**Table 12: Foreseeable Adverse Events and anticipated Adverse Device Effects**

| Adverse Event / Product Effect | Likely Incidence | Mitigation | Recommended treatment |
|---|---|---|---|
| Access failure | Not available | Proper screening of the planned access point with duplex ultrasound and ultrasound-guided vessel puncture | Reattempt from alternative access |
| Access site infection | Not available | Proper surgery preparation and preventive antibiotic treatment | Targeted antibiotic treatment<br>Wound drainage as necessary |
| Allergic reaction to contrast medium or procedure medications | Not available | Appropriate patient screening<br>Appropriate treatment per hospital protocol for known allergy | Appropriate treatment per hospital protocol |
| Allergic reaction to nitinol or other device materials | Not available | Appropriate patient screening | Appropriate treatment per hospital protocol<br>Steroids and referral to immunology/allergy for long-term treatment strategy<br>Possible excision of stent in rare cases (severe allergies) |

| Adverse Event / Product Effect | Likely Incidence | Mitigation | Recommended treatment |
|---|---|---|---|
| Arrhythmia | Not available | Appropriate patient screening | Appropriate arrhythmia treatment per standard of care |
| AV fistula | 0.1% | Ultrasound-guided vascular access<br>User training | Monitor<br>Additional procedure or surgery occasionally required |
| Bleeding | 1.1%* | Stop oral anticoagulants prior to surgery when safe and indicated<br>Appropriate levels of anticoagulant effect with proper dosing and INR for those on warfarin<br>Ultrasound-guided vessel puncture for access-related bleeding | Local manual pressure<br>Transfusion, if needed<br>Additional procedure or surgery occasionally required (i.e. if from pseudoaneurysm for example) |
| Bruising | Not available | Stop oral anticoagulants prior to surgery when safe and indicated<br>Appropriate levels of anticoagulant effect with proper dosing and INR for those on warfarin<br>Ultrasound-guided vessel puncture for access-related bleeding | Monitor |
| Death | 0.0% | Appropriate screening | Not applicable |
| Device breakage | Not available | User training | Additional procedure, surgery |
| Device maldeployment | Not available | User training | Additional procedure, surgery |

| Adverse Event / Product Effect | Likely Incidence | Mitigation | Recommended treatment |
|---|---|---|---|
| Edema | Not available | Limb elevation pre-procedure<br>Physical exercise<br>Compression stockings | Specific treatment of the cause (i.e. lymphedema, heart surgery, stent problem, worsening venous reflux, musculoskeletal injury).<br>Limb elevation<br>Physical exercise<br>Compression stockings<br>Edema therapy<br>Management of coincident lymphedema (lymph pump, lymphedema therapy)<br>Referral to cardiology<br>Medication changes (i.e. stop calcium channel blockers) |
| Fever | Not available | Antipyretics | Antipyretics |
| Hematoma | 3.6%* | Stop oral anticoagulants prior to surgery when safe and indicated<br>Appropriate levels of anticoagulant effect with proper dosing and INR for those on warfarin<br>Ultrasound-guided vessel puncture for access-related bleeding | Local manual pressure<br>Surgical intervention, if needed<br>Transfusion, if needed |
| Hypotension, nausea, or other vasovagal response | Not available | Not applicable | Symptomatic treatment according to standard of care |
| Infection (other than access site) | Not available | Preventive antibiotics | Antibiotics |
| Myocardial infarction | Not available | Appropriate screening | Treatment per standard of care |
| Pain | Not available | Consider preventive analgesics<br>Local anesthesia for periprocedural pain<br>Minimize hematoma formation as described above (Hematoma) | Analgesics |

| Adverse Event / Product Effect | Likely Incidence | Mitigation | Recommended treatment |
|---|---|---|---|
| Pseudoaneurysm | 0.2% | Stop oral anticoagulants prior to surgery when safe and indicated.<br>Appropriate levels of anticoagulant effect with proper dosing and INR for those on warfarin<br>Ultrasound-guided vessel puncture for access-related bleeding | Transfusion, if needed<br>Thrombin injection or surgery if symptomatic, greater than 2 cm or ruptured |
| Pulmonary embolism | 0.2% | Appropriate screening<br>Early mobilization<br>Resumption of anticoagulation in those with a history of DVT/PE | Treatment per standard of care |
| Renal insufficiency/renal failure (new or worsening) | Not available | Periprocedural hydration<br>Hold ACE/ARBs/Diuretics/ Metformin in the morning of surgery<br>Limitation of NSAID use<br>Limitation of contrast administration | Treatment per standard of care |
| Sepsis | Not available | Perioperative antibiotics<br>Standard preparation of the access site | Emergency treatment per standard of care |
| Stent fracture | 1.4% | User training<br>Avoid overlap under the inguinal ligament | Monitor<br>Additional procedure/surgery, if needed |
| Stent malapposition | Not available | User training<br>Appropriate stent sizing<br>Additional post-dilatation | Additional procedure/surgery, if needed |
| Stent malposition | Not available | User training<br>Appropriate stent sizing | Additional procedure/surgery, if needed |

| Adverse Event / Product Effect | Likely Incidence | Mitigation | Recommended treatment |
|---|---|---|---|
| Stent migration | 1.6% | User training<br>Appropriate stent sizing | Additional procedure/surgery, if needed |
| Stroke/paradoxical embolism/transient ischemic attack/intracerebral hemorrhage | Not available | Appropriate screening<br>Use of INR to guide warfarin anticoagulation and avoid supra-therapeutic effect | Treatment per standard of care |
| Tissue necrosis | Not available | Appropriate screening<br>Pre- and post-op care<br>Avoid hematoma | Wound care<br>Surgery, if needed<br>Treatment per standard of care |
| Transfusion reaction following blood transfusion for treatment of major bleeding | Not available | Appropriate screening<br>Avoid bleeding | Treatment per standard of care |
| Vessel damage, including perforation or rupture | Not available | User training | Additional procedure, surgery |
| Venous occlusion/thrombosis, within or outside of stented segment | Not available | Appropriate anticoagulation<br>Avoidance of skip areas between two stents<br>Establishment of adequate inflow and outflow | Appropriate anticoagulation<br>Additional procedure, surgery (percutaneous mechanical thrombectomy, thrombolysis, balloon maceration, additional stenting) |

*The percentages are based on the literature review which represents major bleedings and wound hematoma only.

The list of foreseeable adverse events and anticipated adverse device effects will regularly be updated during the study. The updated list will be kept separate from the Clinical Investigation Plan.

## 12.2 Reporting of Adverse Events

### 12.2.1 Evaluation and Documentation of Adverse Events and Device Deficiencies

Investigators are required to assess and document in the medical record all Adverse Events (AEs) and Device Deficiencies (DDs) (per the definitions in **Table 10**) observed in subjects from the time of enrollment. AEs will be followed until the event has resolved or until study exit. In case of permanent impairment, the event will be followed until the event stabilizes and the overall clinical outcome has been ascertained. Reporting of AEs and DDs will end once the subject exits the study. In case AEs are unresolved at the time of study exit, this will be documented in the eCRF.

The following subjects will be followed for 30 days after the procedure:

- subjects in whom the Abre system did not enter the vasculature during the implant procedure (for example because of not meeting the I/E criteria);
- subjects in whom the Abre system entered the vasculature, but who did not have an Abre stent implanted.

All AEs during this 30 day follow-up period will be handled as per the described study requirements.

All adverse events and device deficiencies (see also **Section 12.2.4**) that occur during this study are required to be reported to Medtronic by completing the Adverse Event or Device Deficiency eCRF, which will be accessible by Medtronic and designees who have authorized access to the EDC system. All reported adverse events will be reviewed by Medtronic or authorized designee to determine whether the adverse event meets regulatory reporting requirements.

The general process for reporting Adverse Events is as follows:

- Report the event to Medtronic as soon as possible, but no later than the timeframes outlined in **Table 14**
- Sites will be provided with the contact information of the appropriate Medtronic authorized designee
- Complete all sections of the Adverse Event eCRF
- Each unique event/diagnosis must be documented separately
- The Adverse Event eCRF must be reviewed and approved by the investigator

The following information should be collected on the Adverse Event eCRF:

- Date of onset or first observation (if full date not available the date when diagnosis was established can be used)
- Date of first awareness by investigator
- Description of the event (single diagnosis term)
- AE code number (provided by Medtronic)
- Seriousness of the event
- Causal relationship of the event to the Abre system
- Causal relationship of the event to the implant procedure
- Action taken, including any medical or surgical intervention and date of intervention
- Narrative (describe any additional details relevant to the AE)
- Outcome or status of the event; any reported event should be followed until it has resolved, has a stable level of sequelae, or is no longer clinically significant in the investigator’s opinion

In addition, for specific endpoint-related adverse eventsas described in the CEC Manual of Operations, sites should submit relevant, de-identified source documents to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication of the event. The CEC may request source documentation on additional events, at their discretion and according to the CEC Manual of Operations. Additional information regarding the CEC is detailed in **Section 13.2**.

### 12.2.2 Reporting of Device Deficiencies

Device deficiencies that led to an AE are reported on the AE eCRF (one for each AE).

Device deficiencies that did not lead to an AE should be reported on a Device Deficiency eCRF (one for each device deficiency).

Device deficiencies that did not lead to an adverse event, but might have led to an SADE if: a) a suitable action had not been taken, or b) an intervention had not been made, or c) circumstances had been less fortunate, should be reported to Medtronic immediately (but no later than 72 hours of the investigator's / site's first knowledge of the event (or sooner if required by local regulation) of the site's first learning of the event on a Device Deficiency eCRF.

Any device or accessory involved with a device deficiency should be returned to Medtronic (unless implanted) for analysis (see **Section 8.9**).

### 12.2.3 Non-Reportable Medical Occurrences

Documented pre-existing conditions or a procedure required by the CIP, are not considered AEs and should not be reported unless there is a change in the nature or severity of the condition. Pre-existing events should be reported as Adverse Events in the situation where a new treatment has to be started or an existing treatment has to be changed to treat the adverse event and the event is accompanied with signs and symptoms.

Unavoidable events are conditions inherent to an endovenous procedure that can potentially occur in each subject for a projected duration according to the investigator's opinion, including, but not limited to the events listed in **Table 13**. Unavoidable events should not be reported unless the event worsens or is present outside the stated timeframe from the endovenous procedure.

**Table 13**: **Unavoidable events**

| Event Description | Timeframe (hours/days) from the endovenous procedure |
|---|---|
| Anesthesia related nausea / vomiting (with or without treatment) | 24/1 |
| Low-grade fever (<100°F or 37.8°C) | 48/2 |
| Pain at access site (with or without standard treatment and subject not returning to clinic to have additional treatment) | 72/3 |
| Mild to moderate bruising / ecchymosis at access site(s) | 168/7 |
| Sleep problems (insomnia) (with or without treatment) | 72/3 |
| Back pain (with or without treatment) | 168/7 |
| Bleeding at access site (not requiring treatment) | 24/1 |
| Longitudinal movement of the stent of less than 1 cm and without clinical symptoms | N/A |

### 12.2.4 Requirements for Adverse Event Reporting

Adverse events and device deficiencies should be reported by the investigator to Medtronic as soon as possible after the event occurs, but no later than the timeframes listed in **Table 14** or local requirements, whichever is more stringent.

In addition, investigators are obligated to report adverse events and device deficiencies in accordance with the requirements of their reviewing Ethics Board and local regulations.

Medtronic is obligated to report adverse events and device deficiencies that occur during this study to the Regulatory Authorities and Ethics Board as per local requirements.

**Table 14: Required Timeframes for Adverse Event reporting by investigator to Medtronic**

| Timeframe for Reporting | Event Type |
|---|---|
| Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event (or sooner if required by local regulation) | • Adverse Device Effect (ADE) or Device Related Adverse Event<br>• Device Deficiency (DD)<br>• Device Deficiency that might have led to an SADE<br>• Serious Adverse Device Effect (SADE)<br>• Serious Adverse Event (SAE)<br>• Unanticipated Adverse Device Effect (UADE)<br>• Unanticipated Serious Adverse Device Effect (USADE) |
| In a timely manner from the investigator's / site's first knowledge of the event | Adverse Event (AE) |

### 12.2.5 Vigilance Reporting

The Abre system will be market released in Europe. All product complaints must be reported for Post Market Surveillance. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements.

- **Product Complaint**: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.
- **Vigilance Reporting:** A system used to notify the Competent Authority (CA) about incidents with regard to medical devices that carry the CE mark. This system requires a manufacturer to notify the competent authority of incidents immediately on learning of them.
- **Incident:** Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or user or of other persons or to a serious deterioration in their state of health.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic regardless whether they are related to intended use, misuse, or abuse of the product. Reporting must be done within 48 hours and per the regular channels for market released products.

### 12.2.6 Emergency Contact Details for Reporting Events and Device Deficiencies

In case of an immediately reportable Adverse Event or in a medical emergency situation, the investigator can contact the Medtronic Study Manager or designee. Contact details of Medtronic Study Management are subject to change and will be maintained in the Investigational Site File and updated contact details will be provided to sites whenever applicable.

# 13 Committees / Core Laboratories

## 13.1 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) is composed of at least four members with pertinent expertise (3 physicians and at least 1 biostatistician) who are not participants or directly involved in the conduct of the study. A minimum of one interventionalist will serve as a member of the DSMB.

The responsibility of the DSMB is to evaluate safety data during the course of the study and to advise Medtronic about the continuing safety of the study, to ensure the well-being of the current participants and those yet to be enrolled as well as the continuing validity and scientific merit of the study.

Based on the safety data, the DSMB may recommend that Medtronic modify or stop the study. DSMB composition, duties, procedures, deliberation rules are detailed and documented in the DSMB Charter.

The Data Safety Monitoring Board will be established and led by:

Syntactx
4 World Trade Center
150 Greenwich Street
New York, New York 10006, USA
Phone: +1-212-228-9000
Fax: +1-646-375-3183

## 13.2 Clinical Events Committee

The Clinical Events Committee (CEC) is made up of clinicians (interventional and non-interventional) with pertinent expertise (i.e. vascular surgeons, interventional radiologists) who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC is charged with the categorization of selected adverse events and clinical endpoints in the study, using criteria established at the outset of the study and specified by the CIP, the CEC Manual of Operations, and relevant societal reporting standards. The CEC Manual of Operations will specify explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify an event.

Database automated alerts and the independent Medical Monitor at Medtronic's designated Contract Research Organization (CRO) will identify clinical events requiring adjudication as specified in the CEC Manual of Operations. The CEC will regularly evaluate and adjudicate these events, as well as other events as may be requested by Medtronic.

The CEC will be established and led by:

Syntactx
4 World Trade Center
150 Greenwich Street
New York, New York 10006, USA
Phone: +1-212-228-9000
Fax: +1-646-375-3183

## 13.3 Duplex Ultrasound Core Laboratory

The Duplex Ultrasonography Core Laboratory (Duplex Core laboratory) is responsible for developing protocol requirements, reviewing DUS exams, interpreting subject DUS data, and providing feedback on the quality of the DUS exams to participating sites. The Duplex Core laboratory will review, analyze, and record data on the Duplex Core laboratory Assessment eCRF. The Duplex Core laboratory's reviewer's interpretation of all DUS exams will be used for the data analyses. All DUS exams will be evaluated by:

VASCORE
The Vascular Ultrasound Core Laboratory
1 Bowdoin Street
Boston, MA 02114, USA
Phone: +1-617-726-5552
Fax: +1-617-726-1977

## 13.4 Venography, X-ray, and IVUS Core Laboratory

The venography, X-ray, and IVUS Core Laboratory is responsible for developing protocol requirements, reviewing and interpreting venograms; X-ray, and IVUS studies, and providing feedback on the quality of the imaging studies to participating sites. The core laboratory will review, analyze, and record data on the applicable Core laboratory assessment eCRF. The core laboratory's reviewer's interpretation of all imagings will be used for the data analyses. All venogram, X-ray, and IVUS recordings will be evaluated by:

Syntactx
4 World Trade Center
150 Greenwich Street
New York, New York 10006, USA
Phone: +1-212-228-9000
Fax: +1-646-375-3183

# 14 Statistical Design and Methods

The clinical performance of the Abre system will be evaluated through a prospective, single-arm, non-randomized, multi-center, global clinical study in a total of 200 included subjects with a hypothesis-based 30-day composite safety endpoint and a hypothesis-based 12-month effectiveness endpoint assessed by performance goals.

Statistical analysis will be performed by Medtronic statisticians or their designated representatives. A separate Statistical Analysis Plan (SAP) has been developed to further describe pre-specified statistical methods, data handling rules, and analyses that will be employed. Any deviation from the original statistical analysis plan will be reported in the final study report, along with justification for the deviation(s).

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. Statistical analyses will be conducted in SAS version 9.4 or above (SAS Institute, Cary, N.C.) or another validated statistical software package.

For adverse event reporting, the primary analysis will be based on subject counts, not event counts. Both subject counts and event counts will be presented in tabular summaries of results, as appropriate.

## 14.1 Performance Goals

### 14.1.1 Performance Goal: Primary Effectiveness Endpoint

The primary effectiveness performance goal endpoint in this study is primary patency. 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 $\pi$ 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. In order to estimate the expected rate of primary patency in the study population at 12 months, the review of the available literature was used (see Appendix A Scientific Literature Search).

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 performance goal for the current study.

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.

### 14.1.2 Performance Goal: Primary Safety Endpoint

The study's primary safety endpoint is defined as a composite of all-cause death occurring post-procedure, clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism, major bleeding complication (procedural), stent-migration and stent thrombosis confirmed by imaging as assessed by core laboratory within 30 days of the index procedure. The review of the literature that provided results on these endpoints suggests an expected rate of 5.6% (see **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:

$H_0$: $P \geq PG$

$H_A$: $P < PG$

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

## 14.2 Sample Size Calculation

Primary Effectiveness: Using the assumptions above on the performance goal and anticipated outcome, we assume desired power of at least 92% under difference 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 difference testing relative to the performance goal 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 performance goals are as follows:

**Table 15**: **Effectiveness and safety performance goals**

| **Endpoints** | **PGs** |
|---|---|
| Primary Patency at 12 months | 75% |
| MAE at 30 days | 12.5% |

## 14.3 Analysis Sets

The primary analysis set will consist of all 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 PMA primary analysis will occur when all 12-month follow-up data have been collected.

For the primary effectiveness endpoint, subjects will be included in the primary analysis when:

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, subjects will be included in the primary analysis when:

a) the subject experiences at least one of the primary safety composite events within 30 days; or
b) stent-migration and stent thrombosis confirmed by imaging as assessed by core laboratory at 30-day visit; 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 whom the denominator for the primary safety endpoint will be the number of implanted subjects who had sufficient follow up (at least 23 days for 30-day visit) plus any subjects who had an event prior to the 30-Day Follow-Up visit.

One interim analysis will be performed on safety for the DSMB. The interim analysis is planned when 30-day follow-up data have been obtained on 30 subjects. The interim analysis does not permit early stopping for effectiveness and therefore no alpha-spending or other adjustment to the study's statistical hypotheses is required. The DSMB Charter may specify additional safety analyses.

Additional exploratory analyses of the data may be conducted as deemed appropriate.

## 14.4 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. 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 considered to be met if the lower limit of the 97.5% one-sided confidence interval of the 12-month patency rate is above 75%. 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.

The primary safety failure rate is calculated as the number of subjects who had an event prior to the milestone visit divided by the number of evaluable subjects who had sufficient follow up (at least 23 days for 30-day visit) plus any subjects who had an event prior to the milestone visit.

Primary safety failure rate and the exact one-sided 97.5% upper confidence limit (UCL) will be reported. The primary safety objective will be considered to be met if the exact one-sided 97.5% UCL is below 12.5%.

## 14.5 Study Success Criteria

The study will be considered a success if both the primary endpoints meet their respective performance goals. For the effectiveness endpoint this translates into observing a one-sided 97.5% lower confidence limit (LCL) of the point estimate above 75% and for the safety endpoint it means observing a one-sided 97.5% upper confidence limit (UCL) below 12.5%.

## 14.6 Handling of Dropouts and Missing Data

For those subjects not evaluable for primary effectiveness endpoint, multiple imputations will be carried out using the logistic regression approach for a dichotomous outcome using PROC MI in SAS for patients 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 imputation model as covariates:

- Age
- Gender
- Race
- Ethnicity
- Diabetes
- Total occlusion
- Venous disease category
- Villalta score at baseline
- CEAP score at baseline
- VCSS class at baseline
- Reference vessel diameter
- Lesion length

If there are relatively few missing data points (e.g., <10%) for a given 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 data points, 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 lower bound of the 97.5% pooled CI will be compared to the effectiveness PG.

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.

## 14.7 Assessment of Data 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. Poolability is assessed 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 enrolling 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. Similar analyses will be conducted on gender. 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
- Coronary Artery Disease (CAD)
- Chronic Obstructive Pulmonary Disease (COPD)
- Myocardial Infarction (MI)
- Hyperlipidemia
- Cerebrovascular Accident (CVA)
- High Blood Pressure (HBP)
- Diabetes
- History of Tobacco Use
- History of Peripheral Artery Disease (PAD)
- Villalta score
- VCSS
- Venous disease category

If there are relatively few missing data points (e.g., <10%) for a given 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 data points, the variable will be excluded from the imputation analysis.

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 inbalance of the study outcome.

## 14.8 Minimizing Bias

Medtronic shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical study.

Selection of subjects, treatment of subjects and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- For sites that are participating in other endovenous stent studies, which may have similar I/E criteria as the ABRE Study, a written process for avoiding selection bias is required.
- Subjects will be screened to confirm study eligibility with defined inclusion/exclusion criteria prior to inclusion. Sites are required to maintain a log of all subjects screened and enrolled for the study.
- Demographics (including race and ethnicity data) and medical history will be collected at baseline in order to later assess possible characteristics that may influence endpoints.
- Data collection requirements and study procedures will be standardized across all geographies.
- All geographies will follow the same version of the CIP and eCRFs.
- No more than 20% of expected inclusions may come from a single site.
- All study investigators will be required to meet the requirements of 21CFR Part 54, Financial Disclosure by Clinical Investigators.
- All study site and Medtronic personnel will be trained using standardized training materials.
- Regular monitoring visits will be conducted to verify adherence to the CIP and source data.
- An independent CEC will be utilized to regularly review and adjudicate reported adverse events.
- An independent DSMB will be utilized to review data, help safeguard the interests of study subjects, and monitor the overall conduct of the study.
- Independent core laboratories will be utilized to interpret imaging results which will be used for the analysis.

# 15 Ethics

## 15.1 Statement(s) of Compliance

The ABRE Study is designed to reflect the good clinical practice (GCP) principles outlined in ISO 14155:2011. These include the protection of the rights, safety, and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation, and the definition of responsibilities of Medtronic and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted.

The study will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the patient informed consent (IC) process, Ethics Board approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.

In the US, the study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56, and 812 and 45 CFR Part 11 and 46.

In addition, the study will be conducted in compliance with 21 CFR Part 11 and 54 in all participating geographies.

Outside US, the study will be conducted in compliance with ISO 14155:2011 and MDD 93/42/EEC will also be followed.

Where applicable, regulatory authority notification/approval will be done/obtained. Investigational sites will not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency and Ethics Board has been obtained (as appropriate).

Additionally, any requirements imposed by a local regulatory agency or Ethics Board shall be followed, as appropriate.

Each site must provide Medtronic with a copy of the investigational site's Ethics Board approval letter and the Ethics Board-approved Informed Consent Form. Ethics Board approval letters must contain the following elements:

- Study Title and the Medtronic Protocol Number;
- Medtronic's Protocol Version (revision letter and/or date of issue);
- A list of the documents reviewed at the meeting covered by the approval letter;
- If applicable, the required interval for the site's continuing review by the Ethics Board; and
- Expiration date, if applicable and/or allowed by the site's system, of the current approval.

If applicable, approvals for the continuation of the study at each investigational site must be kept current in accordance with the Ethics Board's review schedule, but at a minimum, the study must be re-reviewed by the Ethics Board regularly based on local requirements. All site communications to and from the Ethics Board must be forwarded to Medtronic as they are sent/received.

Medtronic will be informed by the Ethics Board and/or the investigator in case any action is taken by an Ethics Board with respect to this investigation.

This study will be publicly registered on www.clinicaltrials.gov prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki.

# 16 Study Administration

## 16.1 Investigator / Investigational Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical study.

An investigator may be included in the clinical study if compliant with the following requirements:

- Investigator is qualified, educated, and has experience documented by at least 10 iliofemoral venous stent placements in the past year, while in total 20 venous stenting cases should have taken place at the site in the past year. For example, has experience with Zilver Vena (Cook Medical), sinus-Venous (OptiMed), Vici (Veniti), or Wallstent (Boston Scientific) stents or any off-label arterial stent.
- Investigator is qualified, educated, has experience with and has the resources available to conduct endovenous IVUS
- Investigator has interest in the Abre Venous Self-expanding Stent.
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions. Investigator is not on the FDA list of investigators who have been disqualified, restricted, or debarred from conducting clinical studies. Investigator has not been excluded from participation in all Federal Health Care programs (e.g. Medicare, Medical, Medicaid).
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study. Each site must have a designated research coordinator assigned to the study.
- Investigator/site has access to an adequate number of eligible subjects. The number of venous stent placements in the center meeting the I/E criteria should allow for an estimated enrollment of 1 subject per month.
- Investigator/site has the ability to comply with applicable Ethics Board and regulatory requirements.
- Site has participated in at least one pre-market study in the last 5 years.
- Lack of potential conflict(s) of interest.
- Anticipated study startup timeline, including contracting and Ethics Board and regulatory submission and approval (if applicable) is acceptable.
- Anticipated competition for same subject population from competitive ongoing studies is at an acceptable rate.

## 16.2 Clinical Trial Agreement

A clinical trial agreement shall be in place, signed by the participating investigational site and/or principal investigator of each investigational site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the clinical investigation plan and subsequent amendments, with a fully executed agreement.

## 16.3 Study Insurance /Subject Indemnification

Medtronic, plc (including all wholly owned subsidiaries) maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the Ethics Board.

Medtronic will provide subject indemnification according to local laws where this study will be conducted.

## 16.4 Subject Compensation

Subjects will not receive any compensation for their participation in this study (including follow-up); however, Medtronic may, at its option, provide reimbursement for participants who will incur extraordinary travel costs related to their participation in the study, including airfare, mileage, or hotel expenses. The participating Institution will make such request(s) in writing to Medtronic (de-identified of participant information), detailing the unusual circumstances and the excessive costs that the participant will incur. Medtronic will evaluate requests on a case-by-case basis, and will notify the Participating Institution of its decision in writing.

## 16.5 Site Activation/Supply of Study Materials

Investigational sites will receive a formal letter of site activation, upon receipt of or completion of the following:

- Curriculum vitae of the principal investigator, sub-investigators, and all key site staff
    - Other relevant documentation for key site staff (i.e. DUS Technicians) is allowable
- A signed research agreement
- Financial disclosure from the investigators
- FDA/Competent Authority approval (as applicable to the geography)
- A copy of the Ethics Board approval letter, along with the voting roster
- The Ethics Board approved patient information and informed consent form
- Documented training of the investigative team
- Delegated Task List
- Lab certificate and lab normal values/ranges
- Confirmation of adequacy of equipment/facilities

Medtronic will control the supply of devices and study materials (i.e. Investigator Site File), and will only ship investigational devices once the above activation criteria are met, and the site receives a formal activation letter from Medtronic.

## 16.6 Monitoring

Monitoring and monitoring oversight will be provided by Medtronic and detailed in a Monitoring Plan separate from this CIP. Representatives of Medtronic (i.e. contractors and authorized designees) may also act as the study monitors to the site. A list of the study monitors will be kept separate from the Monitoring Plan.

The study data will be 100% source document verified at least up to the timepoint that all data are available to assess both primary endpoints.

Findings from each monitoring visit will be provided to the clinical study personnel at the site. Corrective action will be taken to resolve any issues of noncompliance. If Medtronic finds that an investigator is not complying with the executed Investigator Agreement, the Investigational Plan, the applicable laws and regulations, or the requirements of the reviewing Ethics Board, prompt action will be taken to secure compliance. Medtronic will reserve the right to stop shipment of Abre systems, or suspend or terminate the participation of the investigator or the investigational site.

When source data verification is performed, the monitor must have direct access to original source documentation or certified copies of the original source must be provided.

If electronic source documentation is used at the site, the site must provide to the monitor:

- Direct access to the electronic medical record (e.g. the monitor is given a guest password to directly access the system or
- Direct access to the electronic medical record by reviewing alongside appropriate study staff (e.g. a research coordinator) or
- Certified copies of the electronic medical record. The monitor shall verify that he/she has complete access to all original source required for the study (e.g. the monitor does not have a lower level of access to the original source documentation than the research coordinator or principal investigator necessary for the study).

Further details on Monitoring are outlined in the Monitoring Plan.

### 16.6.1 Site Initiation Visit

Medtronic will conduct a site initiation visit prior to first enrollment to prepare the site to conduct the study, as outlined in the Monitoring Plan. Medtronic may conduct investigator meetings in place of, or in addition to on-site initiation visits. Monitors (and/or other Medtronic representatives) will ensure that the PI and study staff (depending on their role in the study):

- Have received and understand the requirements and contents of
    - CIP
    - Patient Information/Informed Consent Form (PI/ICF)
    - Electronic CRFs
    - IFU
    - Any written clinical investigation agreements (as appropriate)
- Have access to an adequate number of Abre systems
- Have been trained in the use of the Abre system
- Are familiar with the responsibilities of the principal investigator

### 16.6.2 Periodic Monitoring Visit

Periodic monitoring visits will be made at all active investigational sites throughout the clinical study to ensure the safety and wellbeing of the subjects, verify that the investigator obligations are fulfilled, and all applicable regulations and guidelines are being followed.

Monitors will review at a minimum:

- Data submitted on eCRFs are complete and accurate with respect to the subject source documentation (see Monitoring Plan for details of requirements)
- Facilities remain acceptable
- Subject informed consent is being obtained and properly documented
- The CIP is being followed
- Complete records are being maintained
- Appropriate and timely reports have been made to Medtronic and/or its authorized designees and the Ethics Board
- Device and Device inventory are controlled
- The investigator is carrying out all agreed activities

- Only authorized individuals are participating in the clinical study
- Any equipment to be used for assessing the clinical investigation variables are maintained/calibrat ed according to the site's standard protocol

### 16.6.3 Study Closure

Upon study completion or at the time a site is terminated, Site Closeout Visits will be conducted, as outlined in the Monitoring Plan.

After the study has been completed, medical care will be provided to the subjects upon the discretion of the treating physician.

## 16.7 Data Management

Study sites will designate a unique subject ID number (SID) at the point of subject enrollment, which is assigned by Medtronic in the EDC system. Records of the subject/SID relationship will be maintained by the study site.

### 16.7.1 Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection. The database is located on a secure server at a Medtronic facility located in the US. All users will be trained on the use of the database prior to obtaining access. Once access is granted, users will have a unique User ID and will create their own password. Data stored electronically shall be maintained in compliance with 21CFR Part 11. The database for this study will be maintained according to corporate policy and record retention schedule.

### 16.7.2 Data Collection

It is the responsibility of the participating investigator to ensure the quality of the data being collected. Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegated Task List. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study.

The investigator (or authorized sub-investigator) will electronically sign each eCRF. The EDC system maintains an audit trail on entries, changes or corrections in eCRFs, once the eCRF is saved as complete. If changes are made to an already signed eCRF, the investigator shall re-sign this eCRF.

### 16.7.3 Data Validation

Medtronic and/or assigned designee will be responsible for the processing and quality control of the data (data management) per the Data Management Plan, which describes the procedures for data review, database cleaning, and issue/resolution of data queries. Data will be collected and stored in a validated, password protected database. Data analysis will be conducted utilizing validated software and analysis programs by qualified biostatisticians.

Study data collected will be monitored and verified against source documents in accordance with ISO14155:2011 guidelines and international standards. Any data discrepancies will be addressed through queries posted within the EDC system.

## 16.8 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. Regulatory bodies, such as the Food and Drug Administration, may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents during monitoring, audits and inspections.

## 16.9 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the site.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

In the US, "Protected Health Information" (PHI) will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the informed consent form. This scenario will be covered in the Patient Information-Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

## 16.10 CIP Amendments

Any revisions or amendments to the CIP or Informed Consent document, along with a statement of justification for the changes, will be submitted to all affected Regulatory Authorities (FDA, Competent Authority) and governing Ethics Boards, according to applicable regulations. All amendments to the CIP shall be agreed between Medtronic and the principal investigator(s). Approval by regulatory agencies and Ethics Board (where applicable) must be obtained prior to implementing a CIP revision at the site.

## 16.11 Record Retention

All study-related documents must be retained for a period of at least two years after market-release in his/her region and after study closure (or longer if required by local law). Medtronic will inform the investigator/site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

## 16.12 Publication and Use of Information

The study will be registered at http://clinicaltrials.gov (and any other database per local requirement) before first enrollment in the study. Study data and results will be made available as required per regulations.

Medtronic, recognizing the seminal importance of this investigation, is committed to the widespread dissemination of all endpoint results. A multisite publication may be prepared for publication in a scientific journal. The publication of the principal results from any single site experience within the study is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the endpoint results, participation of investigators may be solicited for data analysis and abstract and manuscript preparation.

A separate Publication Plan will provide detailed information about the Publication Committee, authorship, publication proposals, and requests for data.

## 16.13 Suspension or Early Termination

### 16.13.1 Planned Study Closure

Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Study Closure is a process initiated by distribution of an initial study closure letter. In all geographies, the study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. For each center, Ethics Board approval renewals are required per local/country regulation until the study closure process is complete at that center.

## 16.13.2 Early Termination or Suspension

Termination of the Study is discontinuance, by Medtronic or by withdrawal of Ethics Board or FDA approval, or local regulatory body of an investigation before completion. This is possible for the whole study, for all centers in a country, or for a single center. Study suspension is a temporary postponement of study activities related to enrollment and distribution of the investigational product(s). This is possible for the whole study, for all centers in a country, or for a single center.

### 16.13.2.1 Criteria for Study-wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study for all centers include but are not limited to:

- AEs and device deficiencies associated with the system or product under investigation which might endanger the safety or welfare of subjects
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (medically/ethically justifiable) where the study is operating under regulatory body authority

### 16.13.2.2 Criteria for Investigator/center Termination or Suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Board approval or annual renewal of the study
- Consistent non-compliance to the CIP (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, etc.)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Study Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Ethics Board suspension of the center
- Fraud or fraudulent misconduct (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

## 16.13.3 Procedures for Planned Study Closure, Termination, or Suspension

Medtronic will promptly inform the investigators of the reasons for a study termination or suspension and inform the regulatory authorities (where required per regulatory requirements).

#### 16.13.3.1 Medtronic-initiated

In the case of study termination or suspension for reasons other than a temporary Ethics Board approval lapse, the investigator will promptly inform the Ethics Board.

In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided.

In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic. Subjects already included should continue to be followed out of consideration of their safety, rights, and welfare.

#### 16.13.3.2 Investigator-initiated

- The investigator will promptly inform:
    - Medtronic and provide a detailed written explanation of the termination or suspension
    - The institution (where required per regulatory requirements)
    - The Ethics Board
    - The subjects and may inform the personal physicians of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension:
    - Subject enrollment must stop until the suspension is lifted
    - Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare

#### 16.13.3.3 Ethics Board-initiated

- The investigator will promptly inform:
    - Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
    - The institution (where required per regulatory requirements)
    - The subjects and may inform the personal physicians of the subjects, with the rationale for the study termination or suspension
- In the case of a study suspension:
    - Subject enrollment must stop until the Ethics Board suspension is lifted
    - Subjects already enrolled should continue to be followed in accordance with Ethics Board policy or its determination that an overriding safety concern or ethical issue is involved

# 17 Records and Reports

## 17.1 Responsibilities of the Investigator

The investigator is responsible for the preparation, review, and signature (as applicable), and retention of the records listed as follows:

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the eCRFs and supporting data (source documentation), including, for example:
    - Signed and dated consent forms
    - Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses' notes
    - All adverse event/device deficiency information
    - A record of the exposure of each subject to the Abre system (e.g., date of implant procedure and follow-up assessment dates)
- Documentation of any deviation from the CIP, including the date and the rationale for such deviation
- Signed Investigator Agreement, signed and dated curriculum vitae of the PI, sub-investigator(s) and key members, signed Delegated Task List
- The approved CIP, PI/ICF and any amendments
- Insurance certificate, where applicable
- Ethics Board approval documentation and voting list
- Sample eCRFs
- Regulatory authority notification and approval documentation
- List of Medtronic/monitor contacts
- List of investigation sites
- Training records
- Disclosure of conflict of interest
- Certification of adequacy of equipment
- Lab certificate/lab normal ranges
- Subject ID and Subject Identification & Enrollment Log
- Medtronic's statistical analyses and clinical investigation report

The investigator may withdraw from responsibility to maintain records by transferring custody to another person, who will accept responsibility for record and report maintenance. The investigator is responsible for the preparation, review, signature, and submission of the reports listed in **Table 16** and **Table 17**. These are also subject to inspection by government agencies and must be retained.

Reports will be submitted to regulatory authorities per local reporting requirements/regulations. For Adverse Event reporting requirements, see **Table 14.**

**Table 16**: **Investigator records and reporting responsibilities applicable to the US**

| **Investigator reports applicable to the US** | | |
|---|---|---|
| **Report** | **Submit To** | **Description/Constraints** |
| Withdrawal of Ethics Board approval | Medtronic | An investigator shall report to Medtronic, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. *(21 CFR 812.150(a)(2)).* |
| Progress report | Medtronic and Ethics Board | An investigator shall submit progress reports on the investigation to Medtronic, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly. *(21 CFR 812.150(a)(3))*. |
| Deviations | Medtronic and Ethics Board | An investigator shall notify Medtronic and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by Medtronic is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required. *(21 CFR 812.150(a)(4))* |
| Failure to obtain IC prior to investigational device use | Medtronic and Ethics Board | If an investigator uses a device without obtaining informed consent, the investigator shall report such use to Medtronic and the reviewing IRB within 5 working days after the use occurs. *(21 CFR 812.150(a)(5))* |
| Final report | Medtronic, Ethics Boards | An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to Medtronic and the reviewing IRB. *(21 CFR 812.150(a)(6))* |
| Other | Ethics Board and FDA | An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))* |

**Table 17**: **Investigator records and reporting responsibilities applicable to Europe**

| **Investigator reports applicable to Europe** | | |
|---|---|---|
| **Report** | **Submit To** | **Description/Constraints** |
| Withdrawal of Ethics Board approval | Medtronic | An investigator shall report to Medtronic, within 5 working days, a withdrawal of approval by the reviewing Ethics Board of the investigator's part of an investigation. *(Medtronic Requirement)* |
| Progress Report | Medtronic and Ethics Board | Provide if required by local law or Ethics Board. (ISO 14155:2011) |
| Deviations | Medtronic and Ethics Board and Regulatory Authority | Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to Medtronic who is responsible for analyzing them and assessing their significance.<br><br>Note: When relevant, Ethics Boards or regulatory authorities should be informed. (ISO 14155:2011)<br><br>An investigator shall notify Medtronic and the reviewing Ethics Board of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. (*Medtronic Requirement)* |
| Final report | Ethics Boards and relevant Authorities | An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to Medtronic and the reviewing Ethics Board. *(Medtronic Requirement)* |

## 17.2 Responsibilities of Medtronic

In conducting this study, Medtronic will have certain direct responsibilities and may delegate other responsibilities to consultants and/or contract research organizations; however, Medtronic remains ultimately responsible for the conduct of the study.

Medtronic will maintain the following records, including but not limited to:

- All essential correspondence related to the clinical study
- Signed Investigator Agreement
- Signed and dated current curriculum vitae for each investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event and device deficiency information
- Device complaint documentation
- All data forms, prepared and signed by the investigators, and received source documentation and core laboratory reports
- CIP, Report of Prior Investigations and subsequent amendments
- Site monitoring reports
- Financial disclosure information
- Study training records for site participants and internal study staff members
- Contact lists of all participating investigators/investigative sites, Ethics Board information, study monitors and Medtronic staff members; Medtronic will maintain these lists and provide updates to the necessary parties.
- Sample of device labeling attached to Abre system
- Insurance certificates
- Ethics Board approval documentation and voting list
- Regulatory authority notification and approval documentation
- Lab certificates / Lab normal ranges
- Statistical analyses
- Clinical investigation report

Medtronic is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed in **Table 18** and **Table 19**.

**Table 18: Medtronic records and reporting responsibilities applicable to the US**

| **Medtronic reports for US** | | |
|---|---|---|
| **Report** | **Submit To** | **Description/Constraints** |
| Premature termination or suspension of the clinical investigation | Investigators, Ethics Board, and relevant authorities | Provide prompt notification of termination or suspension and reason(s). *(*ISO 14155:2011*), (MHLW Ordinance 36, Article 32)* |
| Unanticipated Adverse Device Effect (UADE) | Investigators, Ethics Board, FDA, and relevant authorities | Notification within 10 working days after Medtronic first receives notice of the effect. *(21 CFR 812.150(b)(1))* |
| Withdrawal of Ethics Board approval | Investigators, Ethics Board, FDA, and relevant authorities | Notification within 5 working days after receipt of the withdrawal of approval. *(21 CFR 812.150(b)(2))* |
| Withdrawal of FDA approval | Investigators, Ethics Board, and relevant authorities | Notification within 5 working days after receipt of notice of the withdrawal of approval. *(21 CFR 812.150(b)(3))* |
| Investigator List | FDA | Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))* |
| Progress Reports | Ethics Board and FDA | Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)* |
| Recall and device disposition | Investigators, Ethics Board, relevant authorities, and FDA | Notification within 30 working days after the request is made and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))* |
| Failure to obtain IC | FDA | Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))* |
| Final Report | Investigators, Ethics Board, Regulatory authorities upon request, and FDA | Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and Ethics Boards within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))* |

| **Medtronic reports for US** | | |
|---|---|---|
| **Report** | **Submit To** | **Description/Constraints** |
| Deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate investigator(s), are reported on the case report forms and the final report of the clinical investigation.<br><br>Site specific deviations will be submitted to investigators quarterly. *(*ISO 14155:2011*)* |

**Table 19: Medtronic records and reporting responsibilities applicable to Europe**

| **Medtronic reports for Europe** | | |
|---|---|---|
| **Report** | **Submit To** | **Description/Constraints** |
| Unanticipated Serious Adverse Device Effects (USADE) | Ethics Board, investigators, Competent Authorities | Medtronic will notify investigators and Ethics Board in all geographies as soon as possible, but not later than 10 working days after Medtronic first learns of the effect. |
| Serious Adverse Event (SAE) | Ethics Board, Competent Authorities | Submit to Ethics Board per local reporting requirement. Submit to Competent Authority per local reporting requirement. |
| Serious Adverse Device Effects (SADE) | Ethics Board, Competent Authorities | Submit to Ethics Board per local requirement (ISO 14155:2011). Submit to regulatory authority as per local competent authority reporting timelines. |
| Device Deficiency that might have led to an SADE | Ethics Board, Competent Authorities | Submit to Ethics Board per local requirement. Submit to regulatory authority as per local competent authority requirement. |
| Premature termination or suspension of the clinical investigation | Investigators, Ethics Board, Relevant Authority | Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011) |
| Withdrawal of Ethics Board approval | Investigators, Ethics Board, Relevant Authority | All applicable investigators will be notified only if required by local laws or by the Ethics Board. |
| Withdrawal of Competent Authority approval | Investigators, Ethics Board, and Regulatory Authority | Investigators and Ethics Boards will be notified only if required by local laws or by the Ethics Board. |
| Progress Reports | Ethics Board, Regulatory Authority (if required) | This will be submitted to the Ethics Board and/or Regulatory Authority if required. |
| Final Report | Investigators, Ethics Board, and Regulatory Authority (if required) | The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The principal clinical investigator in each center shall sign the report. (ISO 14155:2011) |

| Medtronic reports for Europe | | |
|---|---|---|
| **Report** | **Submit To** | **Description/Constraints** |
| Deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation.<br><br>Site specific deviations will be submitted to investigators quarterly. (ISO 14155:2011) |
| Significant new information | Ethics Board and Regulatory Authority | Ensure that the Ethics Boards and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO 14155:2011) |

## 17.3 Final Report

Medtronic will provide a final written report of the study results according to applicable regulations, and will include:

- Identification of the device(s)
- Description of the methodology and design of the clinical investigation
- Summary of the deviations from the CIP
- Statistical analysis of the study data
- Critical appraisal of the aims of the study

Medtronic will submit this final report to the PIs for review and comment, and shall document and disseminate discrepant comments to all study PIs. The Lead Principal Investigators will provide their signatures, indicating their agreement with the content of the final report.

All required study reports will be submitted to regulatory authorities and Ethics Boards per local reporting requirements/regulations.

# 18 Report of Prior Investigations of the Device and Justification for the Study

A clinical evaluation has been performed to verify the clinical performance and safety of the Abre stent system, according to their intended use, and that the benefits of the devices outweigh associated risks.

Pre-clinical testings met the defined acceptance criteria in-line with applicable International standards, thereby demonstrating specifications and all acceptance criteria set for the devices. The Report of Prior Investigations requirements will be available in the Investigator's Brochure separate from this CIP.

Risk management activities for the Abre stent system assessed the risk associated with the design, process, and clinical use of the proposed device. It was concluded that any risks identified as part of this activity are considered acceptable by the Medtronic Risk Management Team when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

Based on the assessment of the performance of Abre stent; including the state of the art for endovenous stenting, the benefits of the use of this stent outweigh the associated overall residual risk and confirm the conclusion of the risk assessment that the residual risk associated with the Medtronic Abre stent is deemed to be acceptable.

The use of human subjects is required as part of an IDE clinical study to evaluate the safety and effectiveness of the use of device in humans which includes evaluations that cannot be made using bench testing.

The results from the clinical evaluation and the need for an IDE clinical study evaluating safety and effectiveness of the Abre system use in humans, justifies the conduct of the ABRE Study.

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# 20 Appendices

## Appendix A Scientific Literature Search

**Literature Search Objective and Strategy**

Iliofemoral venous obstruction has been recognized with increasing frequency as the underlying cause of lower extremity symptoms including edema, pain, skin changes and, in advanced cases, ulceration. When the presentation is that of acute deep venous thrombosis (DVT), swelling and pain predominate. By contrast, when the process is chronic the symptoms include skin and subcutaneous tissue changes that can progress to ulceration. The latter pattern of symptoms comprises the post-thrombotic syndrome.

Even today, most patients presenting with acute iliofemoral DVT are treated with anticoagulation alone.[1-3] Patients with post-thrombotic symptoms are often followed with non-interventional management consisting of compression hose and elevation of the extremity. Pharmacologic thrombolysis and mechanical thrombectomy have been used to restore venous patency in the setting of acute DVT, and venous stenting has emerged as a useful intervention to address the underlying venous stenosis in such patients. As well, venous stenting has been employed successfully as a primary intervention in patients presenting with symptomatic chronic iliofemoral venous occlusion or non-thrombotic stenosis.

Despite the increasing use of stents in the venous circulation, most studies have employed stents originally designed for arteries or for biliary indications. For this reason, most publications comprise single-center retrospective series. Prospective, protocol-driven, monitored studies with core laboratory analyses of imaging studies are rare. This observation must be taken into account when assessing the frequency of clinical events; with the possibility of underreporting due to the retrospective nature of data collection.

The objective of this literature search is to provide an up-to-date review of published data on the safety and effectiveness of stenting for iliac and iliofemoral venous disease.[g] Currently, no device is approved for the iliac vein indication in the United States, although several are CE marked and available outside the US. This literature search will evaluate the body of existing literature on the use of predicate stents used in the iliofemoral venous segment, and will include data on stents irrespective of whether or not they were cleared or approved for marketing at the time of the study or thereafter.

Currently, there are several societal guideline documents on the standard of care for the treatment of iliofemoral venous lesions. Most of these are heavily weighted toward the treatment of acute DVT. A guideline document published by the American College of Phlebology in October 2015[4] supplements a 2014 clinical practice guidelines document from the Society of Vascular Surgery and the American Venous Forum for the management of venous leg ulcers,[5] and other earlier societal guideline documents.[6-8] While many of the guideline documents are focused on the management of acute thrombotic venous obstruction, some caveats regarding venous stenting have been included. As well, several review articles have been published, some recently, providing some insight to current practice in the field.[9-15] For the most part, the guideline documents and review articles are based upon data from original research publications. This Scientific Literature Review is limited to a review of these original publications and the data incorporated therein.

[g] For the purposes of this review, the ***iliac venous segment*** is defined as the common iliac vein (CIV) and external iliac vein (EIV), and includes treatment of the most caudal inferior vena cava with a stent to obtain complete coverage of a central common iliac vein lesion. It does not include treatment of isolated IVC lesions or extension of CIV lesions beyond the first few millimeters into the IVC. The ***iliofemoral venous segment*** is defined as the iliac venous segment and the common femoral vein, but does not include disease progressing into the profunda femoral vein or the femoral vein.

The specific objectives of the search include the following:

a) The primary objective of this search is to evaluate the clinical safety and effectiveness of stents used in the iliac and iliofemoral venous segments, including predecessor, equivalent and current devices.
    - Collected data will include the frequency of device-related and certain other adverse events that occur at the index procedure and over follow-up. The effectiveness of the devices will be characterized by the patency rates; primary, primary-assisted and secondary, when available.
    - Safety and effectiveness data will be limited to one-year follow-up in most cases, noting the paucity of longer-term follow-up data in published studies.
    - Performance with respect to symptom resolution and Quality of Life (QoL) is covered in this document to the extent that the original publications included standard measures of symptomatic improvement and QoL. A minority of publications include data on baseline and post-procedure assessment of QoL indices and the number of indices accounts for a relatively small number of publications with outcome on any one index.

b) As a secondary objective of the review, outcome data will be characterized by the presenting clinical scenario; acute, post-thrombotic, or non-thrombotic.[h] Therapeutic outcome may vary considerably in these different categories of presentation, so where possible, evaluations will be subcategorized by presentation.

c) Secondary objectives include the analysis of the natural history of iliac and iliofemoral venous segment disease left untreated or managed medically without the use of balloon angioplasty or implanted devices. While the outcome after medical management of iliofemoral venous obstruction is included in this literature review, acute cases are over-weighted, with a paucity of data on the non-interventional treatment of chronic iliofemoral venous disease.

**Review of Literature Search Results**

This literature review included peer reviewed publications identified by the web-based search strategy with the National Library of Medicine National Center for Biotechnology Information PubMed resource through a search date of October 1, 2016 (**Figure1**).

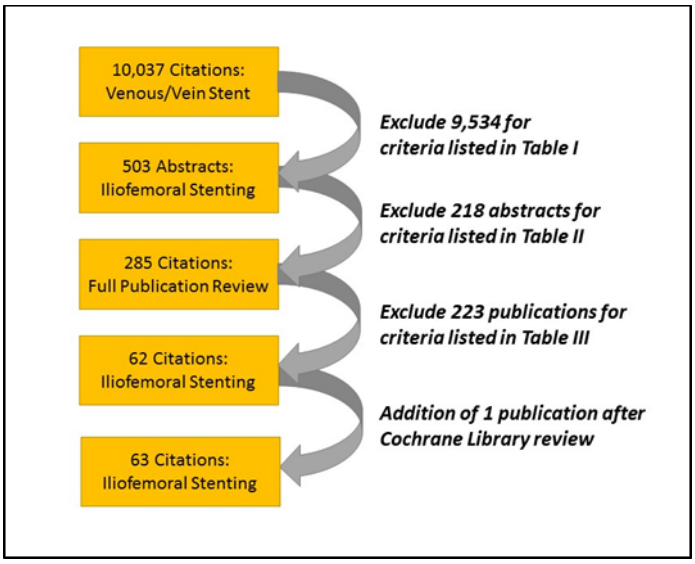


**Figure 1. Search strategy**

[h] For the purposes of this review, the acute subset will be defined when intraluminal thrombus is present and symptoms are of ≤30 days in duration. The post-thrombotic subset includes those patients with a history of deep venous thrombosis in the iliofemoral segment or those where intraluminal thrombotic obstruction is observed on imaging studies with symptoms beginning >30 days prior to presentation. The non-thrombotic subset includes those patients without evidence of intraluminal thrombus. The most common presentation in this group is left central common iliac vein stenosis from the May-Thurner syndrome.

PubMed was the primary source for the review; supplemented with references from review articles published between January 1 and October 1 of 2016.[9,13,14] With one exception, only full original article publications were included in the search results. The exception comprised a non-indexed abstract presented at a scientific meeting but where no manuscript has been published.[16]

The search criteria included the following high-level characteristics:

a) Citations where any field contained the phrase “venous stent” or “vein stent”.

b) Citations where any field contained the word “iliac” or “femoral”.

c) Citations with the word “endovascular” in the title were excluded.[i]

d) Human clinical studies; animal and in vitro studies were excluded.

e) Studies with a sample size of less than ten (10) patients with attempted stenting of the iliofemoral venous segment[j] were excluded.

f) Studies where outcome could not be subcategorized by stented versus non-stented patients were not included.

g) Review articles were not included.

h) When two or more publications reported outcome from the same patients, only the latest (or in some cases the most complete) article was included.

i) Non-English publications were excluded.

The search was repeated twice; once for citations where any field contained the word “iliac” and once for citations containing the word “femoral”. Duplications in these two datasets were removed thereafter, since many citations contained the words iliac ***and*** femoral. Once a list of references meeting the search criteria was identified, each full-length article was obtained. The publications were reviewed; excluding those where stented and non-stented patients were studied but outcome was not stratified by the stented versus non-stented cohorts. In aggregate, the search and selection process was conducted to include all relevant scientific literature, both favorable and unfavorable with respect to iliofemoral venous stenting.

The search strategy results are listed in **Table I**. The search strategies yielded 635 citations; 323 iliac and 312 femoral. Among these, however, there were many duplicates that were identified in the iliac and the femoral searches (search step 3 in **Table I**). After exclusion of the 132 duplicates, 503 abstracts remained.

Next, the text of each of the 503 abstracts were manually reviewed. A total of 218 of 503 abstracts were excluded based on the text of the abstract alone, leaving 285 full publications where review was necessary. After review of each full article, 223 were excluded, based upon the reasons listed in **Table III**). This process left a total of 62 publications appropriate for the iliofemoral venous stenting literature review.

As an added measure to identify pertinent publications, a review of the Cochrane Library was performed (search step 14 in **Table I**). Two searches were performed; one for “venous stent” and one for “vein stent.” A total of 140 and 261 citations were returned, respectively. The titles and/or abstracts of these citations were manually reviewed and 16 potential articles were identified. After review of these 16 articles, one article, a study performed in China, was found to be relevant. This study was included in the literature review, raising the total number of articles on iliofemoral venous stenting to 63.

An additional search of publications on patients with medically-managed iliofemoral venous obstruction was also performed. A total of 9 suitable articles were found; 6 of which comprised publications with stented versus non-stented treatment arms and were already included in the main literature search outlined above. The publications on medical management of iliofemoral obstruction are reviewed separately in this document. Including the 3 additional articles on medical management alone. In sum, a total of 66 articles comprised the full literature search.

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[i] A preliminary review found approximately 100 citations with the word endovascular in the title and almost all were on the topic of endovascular aneurysm repair. The few that were relevant to iliofemoral venous stenting were added back into the search cohort in the manual addition step.

[j] The iliofemoral venous segment is defined as the common iliac, external iliac, and common femoral veins. Patients with stent placement limited to the femoral vein or other veins peripheral to the common femoral vein were excluded from the review. Publications were excluded when iliofemoral and more peripheral stenting was studied but where outcome could not be stratified to estimate results specific to the iliofemoral venous segment.

### Appraisal of literature

Clinical research on the use of stents in the iliofemoral venous segment has, by and large, comprised single-center, retrospective analyses. Few prospective studies have been performed, and randomized clinical trials are non-existent. The preponderance of retrospective studies accounts for a less robust level of evidence than is characteristic of prospective, protocol-based trials. Further complicating the issue, most publications report results from a diverse patient population and do not stratify outcome by category of presentation.

For the purposes of analysis, it has been common to group patients by the presenting clinical category for the procedure. In this regard, patients undergoing iliofemoral venous stenting can be grouped into the following three categories; acute, post-thrombotic, and non-thrombotic.

a) Acute. This category comprises patients presenting with acute iliofemoral DVT. For the purposes of this review, acute has been defined as venous thrombus that has formed within 30 days of treatment. Since it is often impossible to determine the exact timing of the process, acute is defined as the onset of symptoms ≤30 days before treatment, or, in the absence of data on the onset of symptoms, the appearance of acute thrombus on imaging studies has been used as a surrogate.[k] In general, patients presenting with acute DVT were treated with thrombus management technologies such as catheter-directed, intravenous thrombolysis, percutaneous or mechanical or open surgical thrombectomy, followed by deployment of venous stents to address the stenosis unmasked after thrombus removal.

b) Post-thrombotic. The post-thrombotic category comprises those patients who have experienced a thrombotic occlusion of the iliofemoral venous segment but present >30 days after occurrence. In general, such patients present months or years after the DVT which, in many cases, may have gone unnoticed by the patient. Such patients generally have an abundance of collateralization around the occlusion and thrombus, when it remains, is often well-organized and resistant to pharmacologic or mechanical thrombectomy. Patients presenting with post-thrombotic iliofemoral venous occlusion are most often treated with recanalization and stenting alone, without the use of pre-stenting thrombolysis or thrombectomy. Many post-thrombotic patients have an underlying left common iliac vein stenosis (May-Thurner Syndrome) that has gone on to thrombosis, which then propagates to the hypogastric vein orifice, the external iliac vein and/or the common femoral vein.

c) Non-thrombotic. The non-thrombotic category is defined by imaging findings. These patients have a stenosis in the iliofemoral venous segment, usually but not always at the central aspect of the left common iliac vein (May-Thurner Syndrome). This category can be difficult to define with precision, since a significant percentage of the population has a mild to moderate stenosis at the central left common iliac vein. Where inclusion/exclusion criteria of a prospective trial may be able to differentiate symptomatic stenosis from asymptomatic stenosis, retrospective case series without well-defined criteria may include treated patients who may have had lower extremity symptoms from an alternate etiology.

[k] The appearance of intraluminal thrombus on duplex ultrasound, venography, CTV and other imaging studies has not been well-defined. While findings such as an enlarged, occluded vein and an absence of an abundant collateral network are suggestive of an acute process, the literature review could not apply strict criteria to the determination of acute DVT. For this reason, the categorization of the authors was utilized, without modification.

**Table I. Search strategy and initial results**

| Step | Operator | Field | Term | Iliac Search | Femoral Search |
|---|---|---|---|---|---|
| 1 | | All fields | venous stent | 8,894 | |
| 2 | or | All fields | vein stent | 10.037 | |
| 3 | and | All fields | iliac/femoral | 672 | 656 |
| 4 | and | Language | English | 600 | 575 |
| 5 | not | Title | fistula | 544 | 537 |
| 6 | not | Title | aneurysm | 523 | 514 |
| 7 | not | Title | artery | 501 | 453 |
| 8 | not | Title | transplant | 494 | 450 |
| 9 | not | Title | endovascular | 384 | 369 |
| 10 | not | All fields | animal | 323 | 312 |
| Abstracts Identified from Iliac & Femoral Searches | | | | 635 | |
| 11 | Deletions of Duplicates from Iliac & Femoral Searches | | | (132) | |
| Total Abstracts Reviewed | | | | 503 | |
| 12 | Deletions after Review of Abstracts (Table II) | | | (218) | |
| Total Full Publications Reviewed | | | | 285 | |
| 13 | Deletions after review of Full Publications (Table III) | | | (223) | |
| 14 | Addition of Cochrane Publications | | | 1 | |
| **Total Publications Included in Data Analysis** | | | | **63** | |

A total of six groups were defined, as follows:[l,m]

- Group 1: Series with ≥90% of acute cases with post-stenting outcome reported (N = 22)
- Group 2: Series with a mix of acute and chronic (post-thrombotic and/or non-thrombotic) cases, where outcome was not stratified by category of presentation (N = 14)
- Group 3: Series with ≥90% chronic cases but where outcome was not subcategorized by post-thrombotic or non-thrombotic etiology (N = 8)
- Group 4: Series with ≥90% of cases with non-thrombotic etiology (N = 6)
- Group 5: Series with ≥90% of cases with post-thrombotic etiology (N = 18)
- Group 6: Series comprising medically-managed iliofemoral venous obstructions; either as a single publication or as a separately-described treatment arm of a study that includes stented patients (N = 9)

The publications identified in this review were grouped by study design; retrospective vs. prospective, single center vs. multicenter, single-arm vs. dual or multiple arms, and randomized vs. non-randomized. Publications were also categorized by treatment; stented, balloon angioplasty alone, or medical management. Publications that described open surgical thrombectomy with stenting of unmasked lesions were not included in this analysis.

[l] The 6 groups have overlap; some articles report data on more than one indication. Where outcome was stratified by indication, the article is included more than once, with data reported separately for each indication. Where results are not segregated, however, data is reported from the article as a whole (Groups 2 and 3).

[m] The number of stent series is 68, comprising 63 unique stent articles among which four articles reported results from more than a single indication. For example, an article that separately reported outcome of stented patients with a) non-thrombotic and b) post-thrombotic chronic venous obstruction would appear as one article with two series; reported within Groups 4 and 5, respectively. Among the 63 articles, three articles separately reported data from 2 indications (series) and one article separately reported data from 3 indications – for a total of 68 (63 + 5) total stent series.

These numbers do not include series from medically-managed, non-stented patients. In all, there were nine articles that reported data on medically-managed patients. Among these, six articles also separately reported data on stented patients and three reported data on medically-managed patients alone. Therefore, including medically-managed articles/series, the total number of articles in the literature review is 66 (66 + 3) and the total number of series is 77 (68 + 9).

**Table II. Reasons for exclusions among 503 abstracts identified by the search strategy**

| Category of Publication | Publications Excluded | |
|---|---|---|
| | Number | Percent |
| Coronary, heart and valves | 70 | 32.1% |
| Arterial and aneurysms | 57 | 26.1% |
| Stents in upper extremity veins | 26 | 11.9% |
| Hemodialysis access | 14 | 6.4% |
| Trauma (including iatrogenic) | 10 | 4.6% |
| Tumor obstruction of veins | 9 | 4.1% |
| Arteriovenous fistulae/malformation | 6 | 2.8% |
| No stents in series | 5 | 2.3% |
| TIPS and hepatic transplantation | 5 | 2.3% |
| Transplantation (not hepatic) | 4 | 1.8% |
| Vena caval filters | 3 | 1.4% |
| Ureteral stents | 3 | 1.4% |
| Pre-clinical study | 3 | 1.4% |
| Pulmonary embolism/ hypertension | 3 | 1.4% |
| **Total Excluded** | 218 | 100.0% |

**Table III. Exclusion of 163 citations after review of full text**

| Reason for exclusion | Citations (%) |
|---|---|
| Fewer than 10 patients | 89 (39.9%) |
| Reviews and meta-analyses | 28 (12.6%) |
| Overlapping patient series | 20 (9.0%) |
| Outcome not stratified by stented and non-stented patients | 11 (4.9%) |
| Commentaries and editorials | 7 (3.1%) |
| Open surgical revascularization | 6 (2.7%) |
| Treatment of stent complications | 6 (2.7%) |
| Imaging studies and studies without venous stents | 30 (13.5%) |
| Obstruction from tumor or radiation | 5 (2.2%) |
| Traumatic obstruction | 3 (1.3%) |
| Inferior Vena Cava stenting (primary or principal procedure) | 7 (3.1%) |
| Congenital and pediatric series | 3 (1.3%) |
| Animal studies | 3 (1.3%) |
| Guideline documents | 5 (2.2%) |
| **Total Excluded** | **223 (100.0%)** |

**Table IV. Listing of iliofemoral venous stenting publications with key endpoints**

| Reference Number | Lead Author | Publication Year | Indication | Design | N | 1-Year Patency | 30-Day Safety Endpoints | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Mortality | Stent Thrombosis | Stent Migration | Pulmonary Embolism | Major Bleed | Composite MAE |
| **12** | Nayak L | 2012 | Chronic, Post-Thrombotic | Retrospective | 39 | 69.6% | 0.0% | NS | NS | 0.0% | 0.0% | 0.0% |
| **16** | Hager ES | 2012 | Acute | Retrospective | 38 | 94.7% | NS | NS | NS | NS | NS | NS |
| **16** | Hager ES | 2012 | Chronic, Non-Thrombotic | Retrospective | 15 | 100.0% | NS | NS | NS | NS | NS | NS |
| **17** | AbuRahma AF | 2001 | Acute | Prospective | 18 | 83.3% | 0.0% | 16.7% | NS | 0.0% | 11.1% | 27.8% |
| **18** | Alhalbouni S | 2012 | Chronic, Mixed NT & PT | Retrospective | 53 | 48.2% | NS | 3.8% | NS | NS | 1.9% | 5.7% |
| **19** | Bjarnason H | 1997 | Mixed, Acute and Chronic | Retrospective | 29 | 55.3% | NS | NS | NS | 3.4% | 10.3% | 13.8% |
| **20** | Blattler W | 1999 | Chronic, Post-Thrombotic | Retrospective | 14 | 78.6% | NS | 21.4% | NS | NS | NS | 21.4% |
| **21** | Cakir V | 2014 | Acute | Prospective | 14 | 85.7% | NS | 7.1% | NS | 7.1% | NS | 14.3% |
| **22** | Cho H | 2015 | Acute | Retrospective | 48 | 25.0% | NS | NS | 0.0% | NS | NS | 0.0% |
| **23** | de Wolf MA | 2015 | Chronic, Mixed NT & PT | Retrospective | 75 | 96.3% | NS | NS | NS | NS | NS | NS |
| **24** | Delis KT | 2007 | Chronic, Post-Thrombotic | Retrospective | 16 | NS | 0.0% | 6.3% | NS | 0.0% | 12.5% | 18.8% |
| **25** | Gao B | 2011 | Acute | Retrospective | 25 | 92.0% | 0.0% | NS | NS | 0.0% | 0.0% | 0.0% |
| **26** | George R | 2014 | Chronic, Mixed NT & PT | Retrospective | 38 | 97.7% | 0.0% | 2.6% | NS | 0.0% | 0.0% | 2.6% |
| **27** | Husmann MJ | 2007 | Acute | Retrospective | 11 | 90.9% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **28** | Jeon UB | 2010 | Acute | Retrospective | 30 | 83.3% | NS | 3.3% | NS | NS | NS | 3.3% |
| **29** | Juhan C | 2001 | Mixed, Acute and Chronic | Retrospective | 15 | 86.7% | NS | 6.7% | NS | NS | NS | 6.7% |
| **30** | Kim JY | 2006 | Acute | Retrospective | 18 | 88.2% | NS | 0.0% | NS | 0.0% | 5.6% | 5.6% |
| **31** | Knipp BS | 2007 | Chronic, Mixed NT & PT | Retrospective | 58 | 74.1% | 0.0% | NS | 1.7% | 0.0% | 0.0% | 1.7% |
| **32** | Kolbel T | 2007 | Acute | Retrospective | 29 | 80.8% | 0.0% | NS | 5.0% | 0.0% | 6.9% | 11.9% |
| **33** | Kurklinsky AK | 2012 | Chronic, Post-Thrombotic | Retrospective | 89 | 81.3% | NS | 1.1% | NS | NS | NS | 1.1% |
| **34** | Kwak HS | 2005 | Acute | Retrospective | 22 | 95.5% | NS | NS | 4.5% | NS | 4.5% | 9.1% |
| **35** | Kwon SH | 2009 | Acute | Retrospective | 22 | 95.5% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **36** | Lamont JP | 2002 | Mixed, Acute and Chronic | Retrospective | 15 | 100.0% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **37** | Lee KH | 2006 | Acute | Retrospective | 20 | 90.0% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **38** | Matsuda A | 2014 | Chronic, Post-Thrombotic | Retrospective | 13 | 90.9% | 0.0% | 7.7% | NS | 0.0% | 0.0% | 7.7% |
| **39** | Meng QY | 2013 | Acute | Prospective | 45 | 86.7% | 0.0% | NS | NS | 0.0% | NS | 0.0% |
| **40** | Mewissen MW | 1999 | Mixed, Acute and Chronic | Prospective | 99 | 80.8% | NS | NS | NS | 1.0% | 11.1% | 12.1% |
| **41** | Nazarian GK | 1996 | Mixed, Acute and Chronic | Retrospective | 29 | 65.5% | NS | NS | NS | NS | NS | NS |
| **42** | Neglen P | 2007 | Chronic, Non-Thrombotic | Retrospective | 459 | 95.0% | 0.0% | 0.0% | NS | NS | 0.2% | 0.2% |

| Reference Number | Lead Author | Publication Year | Indication | Design | N | 1-Year Patency | 30-Day Safety Endpoints | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **42** | Neglen P | 2007 | Chronic, Post-Thrombotic | Retrospective | 411 | 81.8% | 0.0% | 1.9% | NS | NS | 0.2% | 2.2% |
| **43** | O'Sullivan GJ | 2013 | Mixed, Acute and Chronic | Retrospective | 20 | 85.0% | 0.0% | 15.0% | NS | 0.0% | 0.0% | 15.0% |
| **44** | Park C | 2015 | Acute | Retrospective | 37 | 100.0% | NS | NS | NS | NS | 0.0% | 0.0% |
| **45** | Park JY | 2014 | Acute | Retrospective | 51 | 92.2% | 0.0% | 5.9% | 0.0% | 0.0% | 0.0% | 5.9% |
| **46** | Park SI | 2014 | Acute | Retrospective | 74 | 88.5% | NS | 4.1% | NS | NS | NS | 4.1% |
| **47** | Raju S | 2014 | Chronic, Mixed NT & PT | Retrospective | 210 | 83.9% | 0.0% | 0.0% | 0.9% | NS | NS | 0.9% |
| **48** | Rosales A | 2010 | Chronic, Post-Thrombotic | Retrospective | 34 | 76.5% | NS | NS | NS | NS | NS | NS |
| **49** | Sarici IS | 2013 | Chronic, Post-Thrombotic | Retrospective | 52 | 86.4% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **50** | Semba CP | 1996 | Mixed, Acute and Chronic | Retrospective | 24 | 94.7% | 0.0% | NS | NS | 0.0% | NS | 0.0% |
| **51** | Titus JM | 2011 | Mixed, Acute and Chronic | Retrospective | 36 | 78.8% | 0.0% | 2.8% | NS | 0.0% | 0.0% | 2.8% |
| **52** | Vedantham S | 2004 | Mixed, Acute and Chronic | Retrospective | 18 | 87.0% | 0.0% | 11.1% | NS | 0.0% | 5.6% | 16.7% |
| **53** | Vogel D | 2012 | Chronic, Post-Thrombotic | Retrospective | 10 | 80.0% | 10.0% | 10.0% | NS | 0.0% | 0.0% | 20.0% |
| **54** | Warner CJ | 2013 | Mixed, Acute and Chronic | Retrospective | 32 | 75.8% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **55** | Xue GH | 2014 | Chronic, Post-Thrombotic | Retrospective | 61 | 90.2% | 0.0% | 3.3% | NS | 0.0% | 0.0% | 3.3% |
| **56** | Ye K | 2014 | Chronic, Post-Thrombotic | Retrospective | 110 | 78.1% | 0.0% | 12.7% | NS | 0.0% | 0.0% | 12.7% |
| **57** | Ye K | 2012 | Chronic, Non-Thrombotic | Retrospective | 205 | 98.7% | 0.0% | 0.0% | 1.3% | 0.0% | 0.0% | 1.3% |
| **58** | Liu Z | 2014 | Chronic, Post-Thrombotic | Retrospective | 12 | 81.8% | 0.0% | 0.0% | 0.0% | 0.0% | 8.3% | 8.3% |
| **58** | Liu Z | 2014 | Chronic, Non-Thrombotic | Retrospective | 36 | 96.9% | 0.0% | 0.0% | 8.3% | 0.0% | 0.0% | 8.3% |
| **59** | Hartung O | 2009 | Chronic, Mixed NT & PT | Retrospective | 89 | 89.5% | 0.0% | 2.2% | NS | 0.0% | 2.2% | 4.5% |
| **60** | Lou WS | 2009 | Acute | Retrospective | 44 | 81.8% | 0.0% | 11.4% | 0.0% | 0.0% | 0.0% | 11.4% |
| **60** | Lou WS | 2009 | Chronic, Non-Thrombotic | Retrospective | 38 | 89.5% | 0.0% | 5.3% | 0.0% | 0.0% | 0.0% | 5.3% |
| **60** | Lou WS | 2009 | Chronic, Post-Thrombotic | Retrospective | 29 | 51.7% | 0.0% | 34.5% | 0.0% | 0.0% | 0.0% | 34.5% |
| **61** | Oguzkurt L | 2008 | Mixed, Acute and Chronic | Retrospective | 36 | 75.0% | 0.0% | 2.8% | NS | 0.0% | 0.0% | 2.8% |
| **62** | Patel NH | 2000 | Acute | Retrospective | 10 | 90.0% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **63** | Zhu QH | 2014 | Acute | Prospective | 26 | 96.2% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **64** | Sang H | 2014 | Chronic, Post-Thrombotic | Retrospective | 67 | 83.6% | 0.0% | 4.5% | 0.0% | 0.0% | 0.0% | 4.5% |
| **65** | Wahlgren CM | 2010 | Chronic, Post-Thrombotic | Retrospective | 18 | 62.5% | 0.0% | 16.7% | NS | 0.0% | 0.0% | 16.7% |
| **66** | Gutzeit A | 2011 | Mixed, Acute and Chronic | Retrospective | 13 | 100.0% | NS | NS | NS | NS | NS | NS |
| **67** | Kolbel T | 2009 | Chronic, Post-Thrombotic | Retrospective | 62 | 79.7% | 0.0% | 0.0% | NS | 0.0% | 3.2% | 3.2% |
| **68** | Alernay MB | 2014 | Chronic, Post-Thrombotic | Retrospective | 36 | 78.0% | 0.0% | 8.3% | NS | 0.0% | 0.0% | 8.3% |
| **69** | Ahmed | 2015 | Chronic, Non-Thrombotic | Retrospective | 34 | 67.6% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **70** | Bozkaya | 2015 | Mixed, Acute and Chronic | Retrospective | 21 | 95.2% | NS | 4.8% | NS | NS | 4.8% | 9.5% |

| Reference Number | Lead Author | Publication Year | Indication | Design | N | 1-Year Patency | 30-Day Safety Endpoints | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **71** | Chung | 2016 | Acute | Retrospective | 21 | 83.3% | 0.0% | 0.0% | NS | NS | 4.8% | 4.8% |
| **72** | Ganelin | 2015 | Chronic, Mixed NT & PT | Retrospective | 137 | 97.6% | NS | 2.9% | NS | NS | 0.7% | 3.6% |
| **73** | Jia | 2016 | Acute | Retrospective | 32 | 87.5% | 0.0% | 0.0% | NS | 0.0% | 0.0% | 0.0% |
| **74** | Jiang | 2016 | Acute | Retrospective | 27 | 74.1% | NS | 0.0% | NS | NS | NS | 0.0% |
| **75** | Klitfod | 2015 | Chronic, Post-Thrombotic | Retrospective | 19 | 94.7% | NS | 5.3% | NS | NS | NS | 5.3% |
| **76** | Shi | 2016 | Mixed, Acute and Chronic | Retrospective | 233 | 90.1% | 0.0% | NS | NS | NS | 0.0% | 0.0% |
| **77** | Yin | 2015 | Chronic, Mixed NT & PT | Retrospective | 122 | 82.8% | 0.0% | NS | NS | 0.0% | 0.0% | 0.0% |
| **Weighted Average** | | | | | | **85.7%** | **0.0%** | **2.9%** | **1.4%** | **0.2%** | **1.1%** | **5.6%** |

**Analysis and Discussion of Literature**

The reviewed publications outline the clinical and anatomic characteristics of the population of patients with iliofemoral venous obstruction who were treated with venous stents. In addition 9 publications described the outcome of iliofemoral venous obstruction when treated without intervention; generally with anticoagulation alone. The series that comprised patients followed with medical management alone are reported separately.

**Study Design**

Most publications were single-center, retrospective, non-randomized series (**Table V**). Articles were published between 1996 and 2016 with treatment dates between 1987 and 2014.

**Table V. Study design of publications in final dataset[14]**

| Study Design | Series | Patients | Limbs |
|---|---|---|---|
| Retrospective | 63 (93%) | 3,741 (94.9%) | 4,045 (95.2%) |
| Prospective | 5 (7%) | 202 (5.1%) | 202 (4.8%) |
| Non-randomized | 66 (97%) | 3,884 (98.5%) | 4,188 (98.6%) |
| Randomized | 2 (3%) | 59 (1.5%) | 59 (1.4%) |
| Single-center | 67 (99%) | 3,844 (97.5%) | 4,148 (97.7%) |
| Multicenter | 1 (1%) | 99 (2.5%) | 99 (2.3%) |
| **Total Stent Series** | **68** | **3,943** | **4,247** |

**Clinical Categories of Treated Patients**

Patients undergoing iliofemoral venous stenting are treated for symptomatic outflow obstruction of the lower extremity veins. The symptoms may be acute (<30 days in duration) or chronic. When chronic, the process can be one of occlusion occurring after a silent or asymptomatic iliofemoral DVT (post-thrombotic group) or stenosis in the absence of prior DVT (non-thrombotic group).

Many publications did not subgroup outcome by clinical category. Mixed categories were created to account for such publications. Where a single publication encompassed more than one category but where outcome was grouped, the publication is listed separately in the row for each category. A summary of the frequency of each category of clinical presentation is included in **Table VI**.

There were many more publications on stenting for acute presentations than for the other categories, although these series were characteristically smaller in size. This accounted for a smaller proportion of data on the acute category with respect to patients or limbs. The fewest number of publications were in the non-thrombotic category, although these series were larger, with the greatest average patients/study and limbs/study.

[14] Stent series alone; medical management is reported separately. A single publication may contain more than one series if different cohorts (e.g. acute and post-thrombotic cases) are reported separately.

**Table VI. Number of publications with patients and limbs by indication**

| Clinical Category | Series | Patients | Limbs |
|---|---|---|---|
| Acute | 22 (32%) | 662 (16.8%) | 674 (15.9%) |
| Post-thrombotic | 18 (26%) | 1,092 (27.7%) | 1,185 (27.9%) |
| Non-thrombotic | 6 (9%) | 787 (20.0%) | 865 (20.4%) |
| Mixed, Acute & Chronic[15] | 14 (21%) | 620 (15.7%) | 639 (15.0%) |
| Mixed; PT and NT | 8 (12%) | 782 (19.8%) | 884 (20.8%) |
| **All Series** | **68** | **3,943** | **4,247** |

*PT= post-thrombotic; NT= non-thrombotic.*

*Individual percentages may not add to 100% due to rounding*

**Demographics and Other Baseline Characteristics**

In general, authors specified the patient population by age (mean years), gender, and laterality (left only, right only, bilateral).

**Table VII. Baseline characteristics by publication category[16]**

| Clinical Categories in Publications | Females | Age | Left | Right | Bilateral |
|---|---|---|---|---|---|
| Acute | 65.5% | 56.2 | 87.2% | 9.8% | 3.0% |
| Post-thrombotic | 61.3% | 50.2 | 67.3% | 18.0% | 14.7% |
| Non-thrombotic | 64.6% | 53.9 | 70.6% | 21.7% | 7.7% |
| Mixed, Acute & Chronic | 56.4% | 47.4 | 73.7% | 21.3% | 4.9% |
| Mixed; PT and NT | 68.9% | 55.3 | 60.8% | 28.1% | 11.1% |
| **All Series** | **63.5%** | **52.7** | **70.0%** | **20.4%** | **9.6%** |

*Individual percentages may not add to 100% due to rounding*

[15] Chronic includes both post-thrombotic and non-thrombotic
[16] Weighted averages; by number of patients in each series

**Baseline QoL Indices**

Publications were inconsistent in reporting QoL data at baseline. Most commonly, the Clinical, Etiologic, Anatomic, and Pathologic (CEAP) categories were reported.[78] The CEAP classification was introduced to simplify and standardize the reporting for chronic venous disease. The CEAP definitions were revised in 2004 by a committee of the American Venous Forum. While CEAP is the most frequently reported venous index, both pre- and post-intervention, it does not include subjective complaints and has been criticized as a good index for longitudinal follow-up.[79]

Mean CEAP were reported in some studies and where it was not, the mean CEAP was calculated by a weighted average of the number of limbs in each category. In general, studies were performed for symptomatic limbs with CEAP 2 or greater. The mean baseline CEAP was 3.8 in the studies where it was reported.

**Table VIII. CEAP categories at pre-intervention baseline**

| Clinical Category | CEAP 0-2 | CEAP 3 | CEAP 4 | CEAP 5 | CEAP 6 | Mean CEAP |
|---|---|---|---|---|---|---|
| Acute | 20.3% | 66.7% | 10.1% | 1.4% | 1.4% | 3.0 |
| Post-thrombotic | 4.6% | 44.1% | 26.2% | 7.3% | 18.7% | 3.9 |
| Non-thrombotic | 9.7% | 42.7% | 19.9% | 8.1% | 19.7% | 3.9 |
| Mixed, Acute & Chronic[17] | 5.6% | 69.4% | 22.2% | 0.0% | 2.8% | 3.3 |
| Mixed; PT and NT | 11.3% | 37.8% | 22.4% | 8.0% | 20.6% | 3.9 |
| **All Stent Publications** | **8.7%** | **42.6%** | **22.6%** | **7.5%** | **18.9%** | **3.8** |

**Treatment and Follow-up**

Patients were most commonly treated with the Wallstent, although a wide variety of other stents were used in the studies; particularly in the more recent publications (**Table IX**). Patients were followed for a mean of 24 months after the procedure. Duplex ultrasound was the most frequent imaging modality, although many studies used venography when the duplex study was abnormal and some more recent studies employed computed tomographic venography. Post-procedure anticoagulation varied by the clinical category (indication) for the stent placement, but warfarin was most commonly used; for at least 6 months after stent implantation.

[17] Chronic includes both post-thrombotic and non-thrombotic.

**Table IX. Types of stents used in the series**

| Stent | Series | % of Series[18] |
|---|---|---|
| Wallstent | 44 | 64.7% |
| Luminexx | 14 | 20.6% |
| SMART | 15 | 22.1% |
| Palmaz | 5 | 7.4% |
| Zilver | 5 | 7.4% |
| Protégé | 4 | 5.9% |
| Gianturco | 4 | 5.9% |
| Others | 13 | 19.1% |

*Percentages add to more than 100% since many series use more than one type of stent.*

**Safety Outcomes**

Adverse events were generally tabulated as periprocedural (≤30 days) or later. This review focused on those events that occurred within 30 days of the index procedure. The following occurrences were tabulated: periprocedural (≤30 day) death, major hemorrhage (using the Bleeding Academic Research Consortium, or BARC definition; Types 3a or greater[80]), clinically-evident pulmonary embolism, and access site complications (wound hematoma, false aneurysm and arteriovenous fistula).

The findings suggested that periprocedural death and pulmonary embolism were exceedingly uncommon in the patient populations studied; each occurring in fewer than 1% of patients treated (**Table X** and **Table XI**). The most common events were wound hematoma, stent thrombosis, and stent dislodgement/migration. Major hemorrhagic complications (BARC Type 3a or greater) occurred in approximately 1.1% of patients.

It was often impossible to determine whether major hemorrhagic complications occurred as a result of pharmacologic thrombolytic therapy in those series in which it was employed, accounting for a higher frequency of hemorrhagic complications in series that included patients with acute venous thromboses. Similar findings were evident for wound hematomas. Early (<30 day) stent thrombosis was more common in post-thrombotic cases (4.9%) and was rare in non-thrombotic cases (0.2%). In this literature review, loss of stent patency within 30 days was synonymous with stent thrombosis; no effort was made to differentiate different thrombosis from other causes of occlusion since few publications specified the etiology of the process. Stent migration (exclusive of dislodgement[19]) occurred more often in acute (2.4%) and non-thrombotic cases (2.0%) compared with the other groups (0.8%), possibly related to the absence

[18] Percentages refer to the number of series that reported use of a particular stent. Percentages add to more than 100 since many series used more than a single type of stent.
[19] Dislodgement is defined as stent displacement from the initial deployment site due to catheter/wire/balloon manipulations at the index procedure.

of chronic stenotic disease in these cohorts; where chronic stenoses may have protective effects on the stability of a stent. Neither stent migration or stent dislodgement was reported in any of the post-thrombotic cases.

Adverse occurrences beyond 30 days were also tabulated and included Target Lesion Revascularization (TLR), stent fracture and stent migration. TLR occurred in 8.3% of patients overall through 12 months, and appeared most common in post-thrombotic cases (13.1%). Stent fracture was reported in 1.4% of patients. Stent dislodgement and stent migration were observed in 0.6% and 1.6% of cases, respectively (including migration beyond 30 days).

**Table X. Periprocedural (≤30 day) safety events**

| Clinical Category | Major Hemorrhage | False Aneurysm | Arteriovenous Fistula | Wound Hematoma |
|---|---|---|---|---|
| Acute | 1.8% | 0.0% | 0.7% | 0.4% |
| Post-thrombotic | 0.6% | 0.3% | 0.1% | 1.0% |
| Non-thrombotic | 0.1% | 0.1% | 0.0% | 1.3% |
| Mixed, Acute & Chronic | 3.0%[20] | 0.0% | 0.0% | 17.2%[21] |
| Mixed; PT and NT | 0.8% | 0.3% | 0.0% | 1.6% |
| **All Stent Publications** | **1.1%** | **0.2%** | **0.1%** | **3.6%** |

[20] The high rate of Major Hemorrhage in the Mixed, Acute and Chronic group is skewed the Mewissen series (Radiology,1999) where all patients were treated with thrombolytic agents prior to stenting. Excluding the Mewissen data, the rate of major hemorrhage falls to 0.9% for the Mixed, Acute and Chronic cohort and to 0.7% overall.
[21] The high frequency of wound hematoma is principally a result of the Mewissen series (Radiology,1999) where all patients were treated with thrombolytic agents prior to stenting. Excluding the Mewissen article, the frequency of wound hematoma falls to 2.0% for the Mixed, Acute and Chronic cohort and to 1.2% overall.

**Table XI. Periprocedural (≤30 day) death, pulmonary embolism and stent complications**

| Clinical Category | Death | Pulmonary Embolism | Stent Thrombosis* | Stent Dislodgement* |
|---|---|---|---|---|
| Acute | 0.0% | 0.3% | 3.8% | 0.0% |
| Post-thrombotic | 0.1% | 0.0% | 4.9% | 0.0% |
| Non-thrombotic | 0.0% | 0.0% | 0.2% | 0.0% |
| Mixed, Acute & Chronic | 0.0% | 0.6% | 4.8% | 2.6% |
| Mixed; PT and NT | 0.0% | 0.0% | 1.9% | 1.3% |
| **All Stent Publications** | **0.0%**[22] | **0.2%** | **2.9%** | **0.6%** |

*Reported by number of events per limb, not per patient for stent-related complications

PT= Post-thrombotic

NT= Non-thrombotic

**Table XII. Complications through 12 months**

| Clinical Category | Target Lesion Revascularization | Stent Fracture | Stent Migration[23] |
|---|---|---|---|
| Acute | 4.8% | 0.0% | 2.4% |
| Post-thrombotic | 13.0% | 0.0% | 0.0% |
| Non-thrombotic | Not Specified | 0.0% | 2.0% |
| Mixed, Acute & Chronic | 7.0% | 5.3% | Not Specified |
| Mixed; PT and NT | 4.5% | Not Specified | 1.1% |
| **All Stent Publications** | **8.3%** | **1.4%** | **1.6%** |

[22] The actual weighted average is 0.03%.
[23] Where specified, stent migration included only those events occurring after the index procedure. Stent movement occurring during the index procedure is tabulated as “stent dislodgement” in Table XI.

**Effectiveness Outcomes**

The effectiveness outcomes of the publications comprised technical success and patency rates; primary, primary-assisted and secondary. Technical success at the time of the index procedure was defined differently from study to study. In general, technical success implied successful delivery and deployment of the stent at the intended location without significant residual stenosis. Primary patency was defined as the absence of occlusion or target lesion reintervention. Primary-assisted patency was defined as the absence of occlusion irrespective of whether TLR was performed. Secondary patency was defined when the target lesion was patent irrespective of reintervention, as long as patency was restored. Duplex ultrasound was the most common post-procedure imaging surveillance modality utilized, but many studies also employed contrast venography in follow-up.

Technical success at the index procedure was 95.8% and was highest in non-thrombotic cases (98.8%) and lowest in post-thrombotic cases (92.0%). The primary patency rate for venous stenting was 85.7% at one year (**Table XIII**). Reintervention was often successful when stent stenosis or occlusion occurred, with primary-assisted and secondary patency rates of 93.8% and 95.2%, respectively. Patency rates were highest in patients with non-thrombotic disease (12-month primary patency 94.8%) and lowest in post-thrombotic patients (12-month primary patency 80.5%).

**Table XIII. Patency rates at 12 months after iliofemoral venous stenting**

| Clinical Category (Limbs) | 12-Month Patency Rates | | |
|---|---|---|---|
| | Primary | Primary-Assisted | Secondary |
| Acute (N = 662) | 84.0% | 91.1% | 96.7% |
| Post-thrombotic (N = 1,175) | 80.5% | 88.1% | 91.9% |
| Non-thrombotic (N = 901) | 94.8% | 100.0% | 100.0% |
| Mixed, Acute & Chronic (N = 649) | 83.6% | 85.0% | 93.6% |
| Mixed; PT and NT (N = 958) | 83.8% | 92.9% | 89.5%[24] |
| **All Stent Publications (N = 4,247)** | **85.7%** | **93.8%** | **95.2%** |

[24] Secondary patency for this cohort is lower than primary-assisted patency since different series are included in the two measures.

**Quality of Life Measures after Intervention**

Post-intervention Quality of Life measures were not consistently reported in the studies. The post-intervention CEAP, Villalta, VCSS and CIVIQ-20 scores were reported in only four, six, nine and one of the series, respectively. The VEINES score was not reported in any of the series.

The QoL results indicated improvement from pre- to post-intervention, evident in all four indices studied; as listed in **Table XIV**.

**Table XIV. Pre- and post-intervention venous Quality of Life indices.**

| Scale | Pre-Intervention | Post-intervention | Change |
|---|---|---|---|
| CEAP | 3.8 | 2.2 | 1.6 |
| Villalta | 17.3 | 6.6 | 10.7 |
| VCSS | 9.7 | 3.7 | 6.0 |
| CIVIQ-20[49] | 64 | 83 | 19 |

**Results in Medically-Managed Patients**

There were nine series reporting outcome in patients with iliofemoral venous obstruction after medical management alone.[17,21,39,40,44,77,81-83] A total of 364 subjects and 367 limbs were studied; 58.6% were female with an average age of 48.8 years and mean CEAP 4.2 at presentation. The majority (64.9%) of patients in the medically-managed series were patients with acute iliofemoral venous thrombosis, and the process was on the left in 67.6%, right in 22.9% and bilateral in 9.5%. The follow-up averaged 23 months and, where specified in the publications, the primary treatment modality was heparin follow-up by long-term warfarin anticoagulation. The weighted primary patency rate was 47.1% at 1 year.

**Data from Publications on CE-Marked Stents for the Iliofemoral Venous Indication**

While there are no stents approved for the iliofemoral venous indication in the US, several are CE marked in Europe (**Table XV**). These include the Cook Zilver Vena, OptiMed sinus-Venous, Veniti Vici, and the Boston Scientific Wallstent, The Wallstent, while the most commonly employed stent for two decades, did not receive CE mark for the iliofemoral venous indication until 2015.

It is not possible to parse data on the on-label venous stents from other, off-label venous stents for most of the publications evaluated in the scientific literature review. Authors rarely report results by type of stent. As well, to date (October 2016) there have been no publications on the Veniti Vici stent and Bard Venovo stent. Noting these limitations, the outcome after on-label venous stenting is reported from a small subset of the articles reviewed and is limited to those reports that specify outcome separately for one of the four CE-marked venous stents.

CIVIQ-20 scores were reported in only one publication. Higher scores mean better quality of life.

The findings in the on-label venous stents are dominated by publications that used the Wallstent (**Table XVI**). While this analysis is limited by the relatively small sample size in the on-label group, currently available data do not reveal marked differences between data from studies on CE marked stents compared to those that used other stents.

**Table XV. Venous stents with CE Mark**

| Company | Stent Brand Name | Material | Character | CE Mark |
|---|---|---|---|---|
| Cook Medical | Zilver Vena | Nitinol | Self-expanding | 2011 |
| OptiMed | sinus-Venous | Nitinol | Self-expanding | 2012 |
| Veniti | Vici | Nitinol | Self-expanding | 2013 |
| Boston Scientific | Wallstent | Elgiloy | Self-expanding | 2015[25] |

**Table XVI. Outcome reported from on-label venous stents[26]**

| Stent (Series/Limbs) | Primary Patency | Safety | | | Clinical |
|---|---|---|---|---|---|
| | | 30-day Thrombosis | Stent Fracture | Stent Migration | Villalta Change |
| Cook Zilver Vena (1/20)[43] | 85.0% | 15.0% | NS | NS | NS |
| OptiMed Sinus (1/80)[23] | 96.3% | NS | NS | NS | 6.5 |
| Boston Sci Wallstent (22/2,008) | 88.8% | 1.7% | 1.6% | 2.4% | 7.6 |
| **All CE-Marked Stents (24/2,108)** | **89.0%** | **1.8%** | **1.6%** | **2.4%** | **6.6** |

NS- Not Specified

[25] While an article in Endovascular Today stated that the Wallstent was recently CE marked, there is no confirmation of same on the Boston Scientific corporate website.
[26] There were no publications on the Veniti Vici stent.

**Conclusions**

The results of this Scientific Literature Search suggest that venous stenting was associated with acceptable outcomes in patients presenting with acute, chronic post-thrombotic, and chronic non-thrombotic iliofemoral venous obstruction.

The average age at presentation was 52.7 years, although patients presented throughout all age ranges. Females presented more often than males; 63.5% versus 36.5%, respectively. Treated lesions were more often on the left than the right; 70.0% vs. 20.4%. Bilateral lesions were treated in 9.6% of patients. At baseline, 65.2% of patients were within CEAP 3 or 4 categories; more mild symptomatology was found in 8.7% of cases; 26.4% presented with a healed (C5, 7.5%) or active ulcerations (C6, 18.9%).

The venous stenting procedure was quite safe. Major hemorrhage occurred in 1.1% of patients with access site hematomas in 3.6%. Other access site complications such as false aneurysms or arteriovenous fistulae were very rare as was pulmonary embolism or death within 30 days of the procedure; each occurring in 0.2% or fewer patients. When MAE were defined as the composite occurrence of major procedural bleeding (BARC Type 3a or greater[80]), all-cause mortality, stent thrombosis, pulmonary embolism or stent migration, 5.6% experienced an MAE within 30 days. Stent fracture was reported in 1.4% of patients, with stent dislodgement (at the index procedure) in 0.6% and stent migration (after the index procedure) in 1.6%.

Effectiveness as measured by patency rate was satisfactory. At 1 year, primary, primary-assisted and secondary patency rates were 85.7%, 93.8% and 95.2%, respectively. TLR at 12 months was 8.3%. There did not appear to be substantial differences in outcome between patients treated with off-label or CE-marked venous stents, but the relatively small sample for CE-marked stents precluded a robust analysis.

In summary, iliofemoral venous stenting as reported in the literature appears to be associated with relatively few perioperative and longer-term complications, with a 30-day MAE rate of 5.6% and a primary patency rate of 85.7% at one year.

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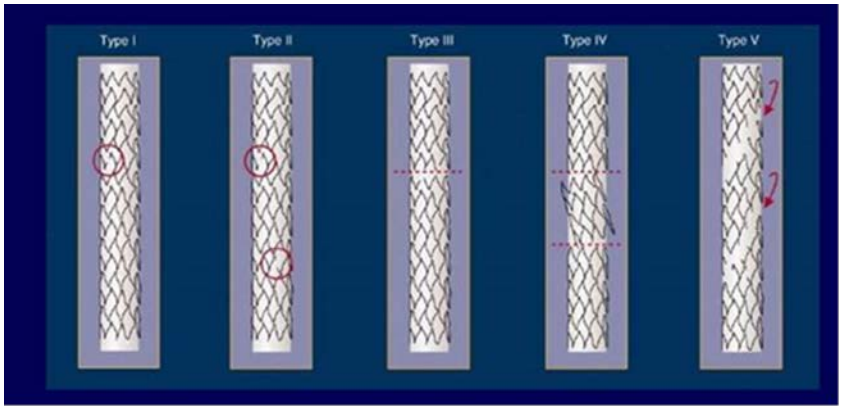
# Appendix B Definitions

| | |
|---|---|
| Acute deep vein thrombosis | Formation of a blood clot (thrombus) in one or more of the deep veins less than 14 days old.<br>Note: this does not include deep venous thrombus contiguous to and occurring as a result of stent occlusion. |
| Acute success | • **Device Success**: Successful delivery and deployment of the Abre stent in the target lesion with successful removal of the delivery system.<br>• **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.<br>• **Procedure Success**: Lesion success without procedure-related MAEs prior to hospital discharge within 30 days.<br><br>Note: If core laboratory is unable to assess the venographic evidence, site reported data will be used. |
| Chronic venous obstruction | Obstruction of the deep veins related to a previous deep vein thrombosis or stenosis from external compression > 6 months before study inclusion. |
| Clinically driven | 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. |
| Major adverse events (primary endpoint) | • All-cause death occurring post-procedure<br>• Clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism<br>• Major bleeding complication (procedural)<br>• Stent thrombosis confirmed by imaging as assessed by core laboratory<br>• Stent migration confirmed by imaging as assessed by core laboratory<br><br>Note: Migration excludes stent dislodgement at the index procedure as may occur with under-sizing of a stent. |
| Major adverse events (secondary endpoint) | • All-cause death occurring post-procedure<br>• Clinically significant (i.e. symptomatic, confirmed by CT pulmonary angiography) pulmonary embolism<br>• Major bleeding complication (post-procedural)<br>• Stent thrombosis confirmed by imaging as assessed by core laboratory<br>• Stent migration confirmed by imaging as assessed by core laboratory<br><br>Note: Migration excludes stent dislodgement at the index procedure as may occur with under-sizing of a stent |
| Major amputation | Surgical removal of tissue in the target limb above the level of the ankle, requiring a prosthetic limb to ambulate:<br>• Above knee amputation (amputation of limb with resection point above the knee)<br>• Below knee amputation (amputation of limb with resection point below the knee and above the ankle) |
| Major bleeding complication | 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. |

| | |
|---|---|
| Major bleeding complication (procedural) | 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 30 days post-index procedure. |
| Major bleeding complication (post-procedural) | 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 at 30 days through 36 months post-index procedure. |
| Minor amputation | Surgical removal of tissue in the target limb:<br>• Trans-metatarsal amputation (amputation with resection point at the level of the metatarsal bones of the foot)<br>• Toe amputation (amputation of one or more toes) |
| Obstructive lesion | Obstructive lesion is defined as:<br>i. Occluded, or<br>ii. ≥50% in diameter reduction on venography or IVUS, or<br>iii. ≥50% area reduction on IVUS |
| Point of enrollment | The point of enrollment is the time at which the subject signs and dates the informed consent form. |
| Point of inclusion | The point of inclusion is the time at which the subject who signed and dated the informed consent form, adhered to all I/E criteria and where the Abre system enters the vasculature. |
| Postthrombotic syndrome (PTS) | Complication of deep vein thrombosis (DVT) or stenosis of a deep vein with symptoms ≥ 6 months before study inclusion. Symptoms may include brownish discoloration of the skin, itching, swelling, slow-healing sores, pain in the area, fragile skin on the area, which may bruise easily, dry or peeling skin. |
| Primary assisted patency | 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.). |
| Secondary patency | Patency of the stented segment of the target lesion after subsequent intervention for an occlusion.<br><br>Note: Confirmed by DUS, evaluated by independent core laboratory. In cases where both DUS and venography were used at the same time point, venography would be used to for the primary assessment. |
| Serious adverse health consequences *(CFR 21-814)* | Any significant adverse experience, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are non-life-threatening and that are temporary and reasonably reversible. |
| Target lesion | The target lesion is defined as 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. |
| Target lesion revascularization (TLR) | Any re-intervention of the stented segment of the target lesion. |
| Target vessel | The target vessel is defined as the common iliac, external iliac and/or common femoral vein. |

| | |
|---|---|
| Stent fracture | Fracture or breakage of any portion of the stent.<br><br>Stent Fracture Classification: Determined by X-ray (assessed by core laboratory):<br>• Type 0 – No strut fractures<br>• Type I – Single tine fracture<br>• Type II – Multiple tine fractures<br>• Type III – Stent fracture(s) with preserved alignment of the<br>• components<br>• Type IV – Stent fracture(s) with mal-alignment of the components<br>• Type V – Stent fracture(s) in a trans-axial spiral configuration<br>  |
| Stent migration | **Stent migration (as part of primary safety and secondary MAE endpoints):** position change of a properly sized venous stent observed with an imaging modality, with displacement of the stent outside of the intended treatment segment after the conclusion of the index procedure, as determined with regard to a reference anatomic structure.<br><br>**Delayed stent migration (as part of secondary endpoint):** 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.<br><br>Stent migration occurs following the proper deployment of a venous stent after the index procedure (i.e. stent movement or dislodgement during the index procedure will not be noted as stent migration). |
| Stent thrombosis | Occlusion of the stented venous segment occurring at any time following stent placement.<br>Stent thrombosis may be diagnosed by Duplex Ultrasound. It needs to be confirmed by venogram or IVUS. |
| Thrombosis | A total occlusion due to thrombus formation as confirmed by sudden onset of symptoms and documented by DUS and venogram and/or IVUS at the target vessel. |
| Vein compression syndrome | A condition in which compression of the common iliac venous outflow tract of the left lower extremity may cause discomfort, swelling, pain, or blood clots |

| | |
|---|---|
| | (deep vein thrombosis) in the iliofemoral vein (also known as the May-Thurner syndrome). |
| Venous occlusive disease | Any pathologic process that occurs from underlying stenosis or occlusion of the veins. |

## Appendix C CEAP Classification

The CEAP classification [39] is a method for evaluating venous disease of the leg based on clinical, etiologic, anatomic, and pathophysiologic data.

The CEAP system consists of two parts: classification and severity scoring:

**Classification**

C- clinical manifestation
E- etiologic factors
A- anatomic distribution
P- pathophysiologic dysfunction

**Severity Scoring**

1. Number of anatomic segments affected
2. Grading of signs and symptoms
3. Disability

**CLINICAL CLASSIFICATION**

C0: no visible or palpable signs of venous disease
C1: telangiectasies or reticular veins
C2: varicose veins
C3: edema
C4a: pigmentation and eczema
C4b: lipodermatosclerosis and atrophie blanche
C5: healed venous ulcer
C6: active venous ulcer

S: symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction.
A: asymptomatic.

**ETIOLOGIC CLASSIFICATION**

Ec: congenital
Ep: primary
Es: secondary (postthrombotic)

**ANATOMIC CLASSIFICATION**

s: superficial veins
p: perforator veins
d: deep veins

**PATHOPHYSIOLOGIC CLASSIFICATION**

Basic CEAP:

Pr: reflux
Po: obstruction
Pr,o: reflux and obstruction
Pn: no venous pathophysiology identifiable

Advanced CEAP:

Same as Basic with the addition that any of 18 named venous segments can be utilized as locators for venous pathology:

*Superficial veins:*

1. telangiectasies/reticular veins
2. GSV above knee
3. GSV below knee
4. SSV
5. Nonsaphenous veins

*Deep veins:*

6. IVC
7. Common iliac vein
8. Internal iliac vein
9. External iliac vein
10. Pelvic: gonadal, broad ligament veins, other
11. Common femoral vein
12. Deep femoral vein
13. Femoral vein
14. Popliteal vein
15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
16. Muscular: gastrocnemial, soleal veins, other

*Perforating veins*:

17. Thigh
18. Calf

# Appendix D Villalta Score

The Villalta Score is a reliable and valid measure of Postthrombotic syndrome (PTS) in patients with previous, objectively confirmed deep vein thrombosis noting responsiveness to clinical change in PTS.

The Villalta score will categorize the severity of PTS.

| **Symptoms/clinical signs** | **None** | **Mild** | **Moderate** | **Severe** |
|---|---|---|---|---|
| Symptoms | | | | |
| Pain | 0 points | 1 point | 2 points | 3 points |
| Cramps | 0 points | 1 point | 2 points | 3 points |
| Heaviness | 0 points | 1 point | 2 points | 3 points |
| Paresthesia | 0 points | 1 point | 2 points | 3 points |
| Pruritus | 0 points | 1 point | 2 points | 3 points |
| Clinical signs | | | | |
| Pretibial edema | 0 points | 1 point | 2 points | 3 points |
| Skin induration | 0 points | 1 point | 2 points | 3 points |
| Hyperpigmentation | 0 points | 1 point | 2 points | 3 points |
| Redness | 0 points | 1 point | 2 points | 3 points |
| Venous ectasia | 0 points | 1 point | 2 points | 3 points |
| Pain on calf compression | 0 points | 1 point | 2 points | 3 points |
| Venous ulcer | Absent | | | Present |

A total score of 0 to 4 indicates no postthrombotic syndrome; score of ≥ 5 indicates PTS. PTS severity: total score of 5 to 9, mild PTS; score of 10 to 14, moderate PTS; and score of ≥ 15 or venous ulcer present, severe PTS.

# Appendix E Venous Clinical Severity Score (VCSS)

Venous disease severity measurement intended to evaluate the responses to changes in disease severity over time and in response to treatment.

| | *None: 0* | *Mild: 1* | *Moderate: 2* | *Severe: 3* |
|---|---|---|---|---|
| **Pain**<br>or other discomfort (i.e. aching, heaviness, fatigue, soreness, burning)<br><br>Presumes venous origin | | Occasional pain or other discomfort (i.e. not restricting regular daily activities) | Daily pain or other discomfort (i.e. interfering with but not preventing regular daily activities) | Daily pain or discomfort (i.e., limits most regular daily activities) |
| **Varicose Veins**<br>"Varicose" veins must be ≥3 mm in diameter to qualify in the standing position | | Few: scattered (i.e., isolated branch varicosities or clusters)<br>Also includes corona phlebectatica (ankle flare) | Confined to calf or thigh | Involves calf and thigh |
| **Venous Edema**<br>Presumes venous origin | | Limited to foot and ankle area | Extends above ankle but below knee | Extends to knee and above |
| **Skin Pigmentation**<br>Presumes venous origin<br><br>Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e., vasculitis purpura) | None or focal | Limited to perimalleolar area | Diffuse over lower third of calf | Wider distribution above lower third of calf |
| **Inflammation**<br>More than just recent pigmentation (i.e., erythema, cellulitis, venous eczema, dermatitis) | | Limited to perimalleolar area | Diffuse over lower third of calf | Wider distribution above lower third of calf |
| **Induration**<br>Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis, hypodermitis)<br><br>Includes white atrophy and lipodermatosclerosis | | Limited to perimalleolar area | Diffuse over lower third of calf | Wider distribution above lower third of calf |

| | | | | |
|---|---|---|---|---|
| **Active Ulcer Number** | 0 | 1 | 2 | ≥3 |
| **Active Ulcer Duration** (longest active) | N/A | <3 mo | >3 mo but <1 y | Not healed for >1 y |
| **Active Ulcer Size** (largest active) | N/A | Diameter <2 cm | Diameter 2-6 cm | Diameter >6 cm |
| **Use of Compression Therapy** | 0<br><br>Not used | 1<br><br>Intermittent use of stockings | 2<br><br>Wears stockings most days | 3<br><br>Full compliance: stockings |

Appendix F EQ-5D

# Health Questionnaire

# English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

**MOBILITY**

| | |
|---|---|
| I have no problems walking | ❑ |
| I have slight problems walking | ❑ |
| I have moderate problems walking | ❑ |
| I have severe problems walking | ❑ |
| I am unable to walk | ❑ |

**SELF-CARE**

| | |
|---|---|
| I have no problems washing or dressing myself | ❑ |
| I have slight problems washing or dressing myself | ❑ |
| I have moderate problems washing or dressing myself | ❑ |
| I have severe problems washing or dressing myself | ❑ |
| I am unable to wash or dress myself | ❑ |

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

| | |
|---|---|
| I have no problems doing my usual activities | ❑ |
| I have slight problems doing my usual activities | ❑ |
| I have moderate problems doing my usual activities | ❑ |
| I have severe problems doing my usual activities | ❑ |
| I am unable to do my usual activities | ❑ |

**PAIN / DISCOMFORT**

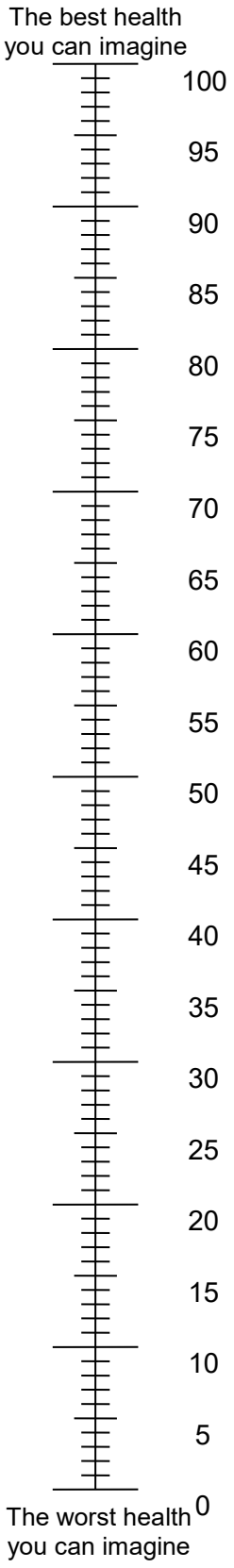
| | |
|---|---|
| I have no pain or discomfort | ❑ |
| I have slight pain or discomfort | ❑ |
| I have moderate pain or discomfort | ❑ |
| I have severe pain or discomfort | ❑ |
| I have extreme pain or discomfort | ❑ |

**ANXIETY / DEPRESSION**

| | |
|---|---|
| I am not anxious or depressed | ❑ |
| I am slightly anxious or depressed | ❑ |
| I am moderately anxious or depressed | ❑ |
| I am severely anxious or depressed | ❑ |
| I am extremely anxious or depressed | ❑ |

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



# Appendix G VEINES-QOL/Sym questionnaire

*VEINES-QOL/Sym English version*

## *VEINES-QOL/Sym QUESTIONNAIRE*

You have had a venous thrombosis. In this survey, we are interested in finding out more about the effects of your leg problem on your daily activities, both at home and at work. This information will give us a better idea about how to treat such problems.

Thank you for participating in this study. This questionnaire includes questions about your health in general and about your leg problem, as well as questions about your life and usual activities. It will take about 10 minutes to complete. All of your answers are confidential. *Do not write your name on the questionnaire.*

Thank you for your help.

*VEINES-QOL/Sym English version*

**INSTRUCTIONS**
**HOW TO ANSWER:**
Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

**These questions are about your leg problem(s).**

**1.** During the past 4 weeks, how often have you had any of the following leg problems?

| | *(check one box on each line)* | Every day | Several times a week | About once a week | Less than once a week | Never |
|---|---|---|---|---|---|---|
| 1. | Heavy legs | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 2. | Aching legs | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 3. | Swelling | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 4. | Night cramps | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 5. | Heat or burning sensation | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 6. | Restless legs | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 7. | Throbbing | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 8. | Itching | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 9. | Tingling sensation (e.g.pins and needles) | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**2.** At what time of day is your **leg problem** most intense ? *(check one)*

☐1 On waking
☐2 At mid-day
☐3 At the end of the day
☐4 During the night
☐5 At any time of day
☐6 Never

**3.** Compared to one year ago, how would you rate your **leg problem** in general now? *(check one)*

☐1 Much better now than one year ago
☐2 Somewhat better now than one year ago
☐3 About the same now as one year ago
☐4 Somewhat worse now than one year ago
☐5 Much worse now than one year ago
☐6 I did not have any leg problem last year

*VEINES-QOL/Sym English version*

**4.** The following items are about activities that you might do in a typical day. Does your **leg problem** now limit you in these activities? If so, how much ?

| | *(Check one box on each line)* | I do not work | YES, Limited A Lot | YES, Limited A Little | NO, Not Limited At All |
|---|---|---|---|---|---|
| a. | Daily activities at work | ☐0 | ☐1 | ☐2 | ☐3 |
| b. | Daily activities at home (e.g. housework, ironing, doing odd jobs/repairs around the house, gardening, etc...) | | ☐1 | ☐2 | ☐3 |
| c. | Social or leisure activities in which you are standing for long periods (e.g. parties, weddings, taking public transportation, shopping, etc...) | | ☐1 | ☐2 | ☐3 |
| d. | Social or leisure activities in which you are sitting for long periods (e.g. going to the cinema or the theater, travelling, etc...) | | ☐1 | ☐2 | ☐3 |

**5.** During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your **leg problem**?

| | *(check one box on each line)* | YES | NO |
|---|---|---|---|
| a. | Cut down the **amount of time** you spent on work or other activities | ☐1 | ☐2 |
| b. | **Accomplished less** than you would like | ☐1 | ☐2 |
| c. | Were limited in the **kind** of work or other activities | ☐1 | ☐2 |
| d. | Had **difficulty** performing the work or other activities (for example, it took extra effort) | ☐1 | ☐2 |

**6.** During the past 4 weeks, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbors or groups? *(check one)*

☐1 Not at all
☐2 Slightly
☐3 Moderately
☐4 Quite a bit
☐5 Extremely

**7.** How much leg pain have you had during the past 4 weeks? *(check one)*

☐1 None
☐2 Very mild
☐3 Mild
☐4 Moderate
☐5 Severe
☐6 Very severe

*VEINES-QOL/Sym English version*

**8.** These questions are about how you feel and how things have been with you during the past 4 weeks as a result of your **leg problem**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

| | *(check one box on each line)* | All of the Time | Most of the Time | A Good Bit of the Time | Some of the Time | A Little of the Time | None of the Time |
|---|---|---|---|---|---|---|---|
| a. | Have you felt concerned about the appearance of your leg(s) ? | ☐1 | ☐ 2 | ☐3 | ☐4 | ☐5 | ☐6 |
| b. | Have you felt irritable ? | ☐1 | ☐ 2 | ☐3 | ☐4 | ☐5 | ☐6 |
| c. | Have you felt a burden to your family or friends ? | ☐1 | ☐ 2 | ☐3 | ☐4 | ☐5 | ☐6 |
| d. | Have you been worried about bumping into things ? | ☐1 | ☐ 2 | ☐3 | ☐4 | ☐5 | ☐6 |
| e. | Has the appearance of your leg(s) influenced your choice of clothing ? | ☐1 | ☐ 2 | ☐3 | ☐4 | ☐5 | ☐6 |

**Thank you for your help.**

Please write today's date: _____/_____/_____ *(day/month/year)*

# Appendix H Center for Medicare and Medicaid Services (CMS) IDE Study Criteria

*Beneficiaries*
Medicare beneficiaries may be affected by the device because in 2014, 57% of the patients diagnosed with venous embolism were Medicare aged. Additionally, 52% of patients treated with a primary diagnosis of venous embolism were of Medicare age. Study results are expected to be generalizable within the Medicare beneficiary population based on the prevalence of venous embolism in patients 65 and older.
*Reference: Truven Health Analytics, MarketScan Inpatient View; 2014*

*Health and Human Services (HHS) Human Subjects Protection Regulations*
All IRBs should comply with 45 CFR Part 46.