Medtronic

Cover page for Study Protocol

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NCT number	NCT03820947
Sponsor trial ID:	MDT18034
Official title of study:	Global, Post-Market, Prospective, Multi-Center, Randomized Controlled Trial of the VenaSeal™ Closure System vs. Surgical Stripping or Endothermal Ablation (ETA) for the Treatment of Early & Advanced Stage Superficial Venous Disease
Document date	31 August 2022

Medtronic Clinical Investigation Plan	
Clinical Investigation Plan/Study Title	VenaSeal Spectrum: Global, Post-Market, Prospective, Multi-Center, Randomized Controlled Trial of the VenaSeal™ Closure System vs. Surgical Stripping or Endothermal Ablation (ETA) for the Treatment of Early and Advanced Stage Superficial Venous Disease
Clinical Investigation Plan Identifier	MDT18034
Study Product Name	VenaSeal™ Closure System
Sponsor/Local Sponsor	**Medtronic Vascular Inc.** 3576 Unocal Place, Santa Rosa, California 95403, United States **Medtronic Bakken Research Center B.V. – EU legal representative** Endepolsdomein 5, 6229 GW Maastricht, The Netherlands **Medtronic Korea Co. Ltd.** 17F, Glass Tower, #534, Teneran-ro, Gangnam-gu, Seoul, 06181, South Korea **Medtronic Australasia Pty Ltd** 2 Alma Road, Macquarie Park NSW 2113, Australia **Medtronic Canada ULC** 99 Hereford St, Brampton Ontario, L6Y 0R3, Canada Telephone number: (905) 460-3800
Document Version	5.0 / 31-AUG-2022
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1. Investigator Agreement and Signature Page

Study Product Name	VenaSeal™ Closure System
Sponsor	Medtronic Vascular Inc. 3576 Unocal Place Santa Rosa, California 95403, United States
Clinical Investigation Plan Identifier	MDT18034
Version Number/Date	5.0 / 31-AUG-2022

I have read the clinical investigation plan, 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 the Declaration of Helsinki, the Clinical Investigation Plan, and Good Clinical Practice, as well as local laws, regulations, and standards, and internal institutional requirements as specified in section 15 of the Clinical Investigation Plan. 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 clinical investigation plan 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.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Table of Contents

2. Glossary

Term	*Definition*
AASV	Anterior Accessory Saphenous Vein
ABI	Ankle-brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
AT	As treated
AVVQ	Aberdeen Varicose Vein Questionnaire
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (English: Federal Institute for Drugs and Medical Devices)
CA	Competent Authority
CE	Conformité Européenne (European Conformity)
CEAP	Clinical, Etiological, Anatomical, and Pathophysiological Classification
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRF	Case Report Form
CTA	Clinical Trial Agreement
CVD	Chronic Venous Disease
DRF	Data Release Form
DTL	Delegated Task List

Term	*Definition*
DUS	Duplex Ultrasound
DVT	Deep Vein Thrombosis
EC	Ethics Committee
EDC	Electronic Data Capture
EGIT	Endovenous glue induced thrombosis
EHIT	Endovenous heat induced thrombosis
EQ-5D-5L	EuroQoL 5 Dimensions Standardized Quality of Life Survey
EVLA	Endovenous Laser Ablation
ETA	Endovenous Thermal Ablation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSV	Great Saphenous Vein
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
ITT	Intention-to-treat

Term	*Definition*
MPSV	Medizinprodukte-Sicherheitsplanverordnung (English: BfArM's Ordinance on the Medical Device Safety Plan)
NRS	Numeric rating scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
NTNTNS	Non-Thermal, Non-Tumescent and Non-Sclerosant
OUS	Outside of the United States
PAD	Peripheral Artery Disease
PASV	Posterior Accessory Saphenous Vein
PE	Pulmonary Embolism
PHI	Protected Health Information
PI	Principal Investigator
PP	Per-Protocol
PPE	Personal Protective Equipment
QoL	Quality of Life
RDC	Remote Data Capture
RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System software
SF-36	Short Form-36 Quality of Life Survey

Term	*Definition*
SFJ	Sapheno-femoral Junction
SoC	Standard of Care
SOP	Standard Operating Procedure
SPJ	Sapheno-popliteal Junction
SSV	Small Saphenous Vein
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
rVCSS	revised Venous Clinical Severity Score
VenousDQoL	Venous Dependent Quality of Life
VenousTSQe	Venous Treatment Satisfaction Questionnaire- early
VenousTSQs	Venous Treatment Satisfaction Questionnaire- status
VLU	Venous Leg Ulcer
VRD	Venous Reflux Disease

3. Synopsis

VENASEAL SPECTRUM Study Synopsis	
Title	VENASEAL SPECTRUM: Global, Post-Market, Prospective, Multi-Center, Randomized Controlled Trial of the VenaSeal™ Closure System vs. Surgical Stripping or Endothermal Ablation (ETA) for the Treatment of Early and Advanced Stage Superficial Venous Disease
Clinical Study Type	Global, post-market, prospective, multi-center, randomized controlled trial
Product Name	VenaSeal™ Closure System, Surgical Stripping and Endothermal Ablation (ETA)
Sponsor/Local Sponsor	**Medtronic Vascular Inc.** 3576 Unocal Place Santa Rosa, California 95403 United States **Medtronic Bakken Research Center B.V.** Endepolsdomein 5 6229 GW Maastricht The Netherlands **Medtronic Korea Co. Ltd.** 17F, Glass Tower, #534 Teneran-ro, Gangnam-gu, Seoul, 06181 South Korea **Medtronic Australasia Pty Ltd** 2 Alma Road Macquarie Park NSW 2113 Australia **Medtronic Canada ULC** 99 Hereford St Brampton Ontario, L6Y 0R3 Canada Telephone number: (905) 460-3800
Indication in Study	The VenaSeal™ closure system will be used according to the instructions for use (IFU) criteria as applicable per geography. ○ United States (U.S.) Indication (VS-402, VS-404): The VenaSeal™ system is indicated for use in the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV), through endovascular embolization with coaptation. The VenaSeal™ system is intended for use in adults with clinically symptomatic venous reflux as diagnosed by duplex ultrasound (DUS).

	○ Outside of the United States (OUS) Indication (VS-403, SP-101): The VenaSeal™ system is intended for the permanent, complete, endovascular adhesive closure of the GSV and associated varicosities in the treatment of venous reflux disease (VRD). ○ South Korea Indication (SP-101): The VenaSeal™ system is intended for use in patients with venous reflux disease as diagnosed by duplex ultrasound (DUS). The VenaSeal™ system is indicated for use in the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV), through endovascular adhesive closure. The indications listed here are at the time of protocol finalization. Please refer to the respective Instructions for Use for current and applicable indications.
Product Status	The VenaSeal™ system is commercially available in all countries selected for participation in this study. Surgical stripping or ETA will be designated comparators when commercially available at a site.
Investigation Purpose	**Randomized Studies (CEAP 2-5):** To evaluate the patient's experience and clinical improvement after treatment with the VenaSeal™ system compared to standard of care treatments, surgical stripping or ETA, in the treatment of symptomatic superficial venous disease (CEAP 2-5). Patient-centered outcomes, vein closure, ability to return to work, and clinical improvement will be measured after treatment of symptomatic venous reflux in the superficial truncal veins by the VenaSeal™ system or the comparator treatments. **VLU Study (CEAP 6):** To evaluate the patient's experience and clinical improvement after treatment with the VenaSeal™ system in the treatment of active venous leg ulcer (VLU) (CEAP 6) subjects.
Target Population	**Randomized Studies (CEAP 2-5):** Adults with symptomatic venous reflux in the superficial truncal veins (CEAP 2-5) appropriate for treatment with the VenaSeal™ system and ETA in VenaSeal vs. ETA Study, and appropriate for treatment with the VenaSeal™ system and surgical stripping in the VenaSeal vs. Surgical Stripping Study. A trial center should provide VenaSeal™ system treatment, and surgical stripping or ETA as part of their standard of care. **VLU Study (CEAP 6):** Adults with symptomatic venous reflux in the superficial truncal veins (CEAP 6) appropriate for treatment with the VenaSeal™ system. Patients will be enrolled globally at up to 40 centers.
Study Design	Global, post-market, prospective, multi-center randomized controlled trial of patients with symptomatic superficial venous disease, with a single arm embedded ulcer subgroup. Expected total enrollment of approximately 500 subjects in VenaSeal Spectrum Study. Approximately 375 subjects will be enrolled in CEAP clinical classifications 2-5

	in the Randomized Studies (108 subjects in VenaSeal vs. Surgical Stripping Study and about 264 subjects in VenaSeal vs. ETA Study), and up to 125 CEAP 6 subjects with VLUs will be treated with the VenaSeal™ system. Enrollment of the VenaSeal vs. Surgical Stripping Study was closed on 22-Feb-2022.
Primary Objective(s)	For the CEAP 2-5 Randomized Studies, the primary objectives are to compare the VenaSeal™ system to surgical stripping and ETA regarding patient experience and satisfaction, through a validated, patient-centered 2-part venous treatment satisfaction questionnaire (VenousTSQ-early [VenousTSQe] and VenousTSQ-status [VenousTSQs]) at 30 days, and the ability to achieve elimination of clinically relevant superficial truncal disease in the target veins at the index procedure. For the VLU Study, the primary objective is to evaluate time to ulcer healing through 12 months.
Secondary Objective(s)	The key secondary objectives are to compare the VenaSeal™ system to surgical stripping and ETA in achieving the anatomical closure of superficial truncal veins at 6 months, and the ability to return to work post-index procedure. The secondary objective of the study is to evaluate the VenaSeal™ system in the treatment of symptomatic venous reflux in the superficial truncal veins. Specific areas of analysis include: effectiveness, safety, healthcare utilization, patient experience, and treating physician experience. In addition, secondary objectives in the VLU Study include ulcer healing rate, ulcer recurrence, and ulcer-free time.
Primary Endpoints	The CEAP 2-5 Randomized Studies have three primary endpoints comparing the VenaSeal™ system to surgical stripping or ETA. 1. Peri-procedural patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days. 2. Patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days. 3. Elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure as measured by the percentage of target vein length successfully treated. The primary endpoint for the VLU Study is time to ulcer healing, calculated through healing confirmation and verified by an independent core laboratory through 12 months.
Key Secondary Endpoints	Data supporting the following endpoints will be collected for both the Randomized Studies as well as the VLU Study. The following endpoints will be compared for the

	Randomized Studies and will be evaluated for the VenaSeal™ system for the VLU Study. 1. Anatomic closure of the primary target superficial truncal vein at 6 months, defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm after VenaSeal™ system and ETA procedures, or the absence of refluxing or residual primary target vein after surgical stripping procedures. 2. Time to return to work as reported by the patient.
Secondary Endpoints	Data supporting the following endpoints will be collected for both the CEAP 2-5 Randomized Studies as well as the VLU Study. When appropriate, data will be evaluated for the CEAP 2-5 Randomized Studies to compare the VenaSeal™ system to surgical stripping or ETA. Data may also be pooled for all VenaSeal™ system subjects from the CEAP 2-5 Randomized Studies and VLU Study as appropriate. Data from VenaSeal vs. Surgical Stripping Study will be collected through the 12 months visit. <u>Effectiveness secondary endpoints</u>

	1. Anatomic closure of primary target vein at 30 days, and 12, 24, 36, 48 and 60 months: • For subjects treated with the VenaSeal™ system or ETA it is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm. • For subjects treated with surgical stripping this is defined as absence of refluxing or residual vein at 30 days and 12 months only. 2. Anatomic closure of target vein at 30 days, and 6, 12, 24, 36, 48 and 60 months: • For subjects treated with the VenaSeal™ system or ETA this is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm. • For subjects treated with surgical stripping this is defined as absence of refluxing or residual vein at 30 days, 6 and 12 months only. 3. Technical success of each target vein immediately post-index procedure: • For subjects treated with the VenaSeal™ system or ETA this is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm. • For subjects treated with surgical stripping this is defined as absence of refluxing or residual vein. 4. Reintervention of any target vein (including primary target vein) through 60 months, assessed at each follow-up visit. Subjects enrolled in the VenaSeal vs. Surgical Stripping Study will be followed through the 12 months visit only. 5. Time to reintervention of any target vein (including primary target vein) through 60 months, as measured by the time between the index procedure and the first reintervention procedure. Subjects enrolled in the VenaSeal vs. Surgical Stripping Study will be followed through the 12 months visit only. <u>Safety secondary endpoints</u> 6. Adverse events (AEs) occurring in the target limb, evaluated from index procedure through 12 months: • Hypersensitivity to VenaSeal™ adhesive • Phlebitis • Granuloma

	• Endovenous glue induced thrombosis (EGIT) or endovenous heat induced thrombosis (EHIT) • Symptomatic deep vein thrombosis (DVT) events 7. Additional events evaluated through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study) • Symptomatic Pulmonary embolism (PE) • Serious adverse events (SAEs) <u>Healthcare utilization secondary endpoints</u> 8. Number and type of adjunctive treatments conducted through 12 months post-index procedure. 9. Healthcare utilization related to the target limb VRD, as determined by the number of healthcare visits conducted, and other health-related resources utilized (e.g., home healthcare services) between study visits through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study). 10. Procedures, tests and treatment of AEs related to the treatment modality or index procedure through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study). 11. VLU Study: Healthcare utilization and routine wound care treatments between study visits through 60 months. <u>Patient Experience secondary endpoints</u> 12. Time to return to normal activities as reported by the patients. 13. Intra-procedural and post-procedural pain at the index procedure, and pain at 7 and 30 days as reported by the patient using the numeric rating scale (NRS) with a scale of 0-10. 14. Change in venous disease symptoms at 7 and 30 days, and at 6, 12, 24, 36, 48, and 60 months compared to baseline (7 and 30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study), as measured by the revised Venous Clinical Severity Score (rVCSS) and subject self-reporting. 15. Change in AVVQ score at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline. 16. Change in EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) at 30 days, and 6, 12, 24, 36, 48 and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline.

	17. Change in the 36-Item Short Form Health Survey (SF-36) reported by the patient at 30 days, and 6 and 12 months compared to baseline. 18. Change in the Venous Dependent Quality of Life (VenousDQoL) reported by the patient at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline. <u>Provider Experience secondary endpoint</u> 19. Provider experience will be assessed post-index procedure, evaluating overall satisfaction with the procedure. **VLU Study:** The primary endpoint of the VLU Study is referenced above. The following ulcer-specific effectiveness endpoints will be evaluated: 20. Ulcer healing rate, as measured by the percentage of the ulcer area healed per given time period, according to an independent core laboratory through 24 months or until ulcer healing has been confirmed. 21. Ulcer recurrence on the target limb, assessed at all follow-up timepoints following ulcer healing through 60 months. 22. Ulcer-free time, calculated as days between initial ulcer healing and first ulcer recurrence, as applicable, through 60 months. In addition, the primary endpoints and any other applicable endpoints of the Randomized Studies will be also assessed for the VLU Study: 23. Peri-procedural patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days. 24. Patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days. 25. Elimination of clinically relevant superficial truncal disease in target vein at the time of index procedure as measured by the percentage of target veins successfully treated.
Follow-up	Follow-up will occur at 7 and 30 days and 6, 12, 24, 36, 48, and 60 months post-index procedure (7 and 30 days, 6 and 12 months for VenaSeal vs. Surgical Stripping Study). CEAP 6 subjects will have additional follow-up visits until healing verification at: 2, 3, 4, 5, 8, and 10 months. If healing has not occurred by 24 months, subjects will continue to follow standard wound care and remaining study visits. Subjects will

	come in for ulcer healing verification visit up to 24 months, after which no core laboratory ulcer assessment for wound healing will be required.
Study Duration	Approximately 8 years, including up to 60-month follow-up post-procedure.
Randomization	CEAP 2-5 subjects will be enrolled via randomization in one out of the two Randomized Studies: 1. VenaSeal vs. ETA Study: subjects will be 1:1 randomized to VenaSeal™ system or the ETA treatment. 2. VenaSeal vs. Surgical Stripping Study: subjects will be 1:1 randomized to VenaSeal™ system or surgical stripping treatment. Each site will be designated as participating in only one of the two Randomized Studies and cannot participate in both. Which study the site will enroll into is pre-determined by geographical region and device/treatment availability. CEAP 6 subjects will not be randomized.
Sample Size	~375 CEAP 2-5 subjects (randomized to VenaSeal™, surgical stripping or ETA treatment) and up to ~125 CEAP 6 subjects (VenaSeal treatment only) at up to 40 global sites.
Inclusion/ Exclusion Criteria	<u>Inclusion:</u> 1. Patient is ≥18 years of age. 2. Patient has venous reflux in superficial truncal vein(s) (e.g., GSV, SSV, accessory saphenous veins) with CEAP category 2 (symptomatic) or CEAP category 3, 4a, 4b, 5, 6 based on the American Venous Forum CEAP classification (2004), appropriate for treatment, as confirmed by DUS. 3. Eligibility for treatment: • VenaSeal vs ETA Study: Patient is eligible for treatment with the VenaSeal™ system and ETA. • VenaSeal vs Surgical Stripping Study: Patient is eligible for treatment with the VenaSeal™ system and surgical stripping. • VLU Study: patients should be eligible for treatment with the VenaSeal™ system. 4. Treatable refluxing segment of target vein(s) 10 cm in length or longer. 5. Patient has a target vein diameter of ≥3 mm throughout the intended treated segment of the target vein as measured by DUS while patient is standing. 6. Patient is willing and capable of complying with specified follow-up evaluations at the specified times. 7. Patient has an ability to understand the requirements of the study and to provide informed consent. <u>Exclusion:</u>

	1. Patient has a known history of allergic sensitivities (including but not limited to cyanoacrylate adhesives), or any other condition, which in the opinion of the investigator may make the patient more susceptible to cyanoacrylate adhesive hypersensitivity. 2. Patient has known deep vein obstruction in the target limb, as identified by the site's standard of care. 3. Patient has abnormal pulse exam or ABI <0.8. 4. Patient has acute superficial thrombophlebitis. 5. Patient requires any non-target vein treatments in the contralateral or ipsilateral limb, or any other surgical procedure up to 30 days pre-procedure and through 3 months post-procedure. 6. Patient has any 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). 7. IFU contraindications: • VenaSeal vs. ETA Study: Patient has VenaSeal™ system and/or ETA product's IFU contraindication(s). • VenaSeal vs Surgical Stripping Study: Patient has surgical stripping and/or VenaSeal™ system IFU contraindication(s). • VLU Study: Patient has VenaSeal™ system IFU contraindication(s). 8. Patient is non-ambulatory. 9. Patient is a female of childbearing potential who may be pregnant or breastfeeding at the time of the index procedure. * 10. 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. 11. Patient is currently participating in an investigational drug or device study when the data collected could be conflicting or biased due to participation in another study. 12. Patient has documented COVID-19 infection currently or within the past 3 months. Patient is not completely recovered from past COVID-19 infection, per physician's discretion. 13. VLU Study: Patient has target ulceration identified to be of non-venous etiology, as confirmed by the independent core laboratory. 14. VLU Study: Patient has target circumferential ulceration that cannot be captured in a single photograph (any ulcer curvature around the leg that goes out of sight). Note: CEAP 6 patients are excluded at sites not identified as VLU sites. *Pregnancy to be assessed per treating physician's routine practice; testing is not required if verbal confirmation is preferred. Breastfeeding patients may be included if mother's expressed milk is discarded surrounding the index procedure, per the

	treating physician's standard instructions. Sites must document routine methods utilized for such patients.

Study Procedures and Assessments

Table 1: Schedule of Assessments – All Subjects

Data Collection Requirement	Screening	Baseline (<30 days before procedure)	Index Procedure (Day 0)	Day 7 (± 2 days)	Day 30 (± 7 days)	3+ Months Adjunctive Therapy (Optional)	6 Months (± 4 weeks)	12 Months (± 8 weeks)[1]	24, 36, 48 and 60 Months (± 8 weeks)	Unscheduled[2]
Informed Consent	X									
CEAP Clinical Classification (2004 and 2020)	X						X	X	X	X
Randomization	X									
Demographics, Medical History		X								
Concomitant Medications		X	X							
rVCSS		X		X	X		X	X	X	X
Patient-Reported Symptoms		X		X	X		X	X		
EQ-5D-5L QoL		X			X		X	X	X	
AVVQ QoL		X			X		X	X	X	
SF-36 QoL		X			X		X	X		
VenousTSQ[3]					X		X	X		
Duplex Ultrasound		X[4]	X	X	X		X	X	X	X
Procedure-related Data & Outcome			X							
Physician Satisfaction with Procedure			X							
Patient-Reported Outcomes				X	X		X	X	X	
Reintervention Review				X	X		X	X	X	
Healthcare utilization				X	X		X	X	X	
Adjunctive Therapy Assessment						X	X	X	X	
Adverse Event Assessment			X	X	X	X	X	X	X	X

Device Deficiency Assessment			X							

[1]Subjects in VenaSeal vs. Surgical Stripping Study will be followed through 12 months only.
[2]AE assessments at unscheduled visits are required. Additional assessments are per investigator's discretion; see section 10.11 for additional detail
[3]VenousTSQe captured at 30 Days; VenousTSQs captured at 30 Days, 6 Months and 12 Months
[4]Sites to utilize their standard of care DUS to assess screening criteria, within 6 months of the Screening/Baseline visit; if not conducted in a standing position, sites will need to re-image patient for target vein measurements only

Data will be collected at the timepoints specified in **Table 1** for all subjects and collected at the timepoints specified in **Table 2** for VLU subjects only.

Table 2: Additional Schedule of Assessments – VLU Study

Data Collection Requirement	Screening	Baseline	Procedure	7 & 30 Days	2, 3, 4, & 5 Months (+/- 7 days)	6 Months	8 & 10 Months (+/- 2 weeks)	12 Months	24, 36, 48, & 60 Months	Healing Verification (<2 weeks of healing)
All-Subject Requirements and Visit Windows from Table 1	*X*	*X*	*X*	*X*		*X*		*X*	*X*	
Etiology Photograph	X									
Target Active Ulcer Assessment		X		X	X	X	X	X		
Ulcer-specific Healthcare Utilization				X	X	X	X	X	X	X
Active Ulcer or Healing Verification Photograph		X[1]		Photographs captured at each visit until healing is demonstrated through 24 months.						X[2]
Adverse Event Assessment			X	X	X	X	X	X	X	X
Ulcer Healing and/or Recurrence Assessment				X	X	X	X	X	X	X
Active Ulcer Wound Care	Wound care and compression therapy to proceed per routine care until healing is demonstrated.									

[1]Index procedure should occur within 7 days of baseline ulcer photograph. If the baseline visit is more than 7 days out from the index procedure, photographs should instead be taken on the day of the index procedure, prior to the start of the procedure.
[2]Healing verification to be captured through 24 months, as applicable.

Statistics	This evaluation has been designed as a global, post-market, prospective, multi-center, randomized controlled study of patients with symptomatic superficial venous disease, with a single arm embedded ulcer study. The study is designed with two Randomized Studies (VenaSeal vs. Surgical Stripping Study and VenaSeal vs. ETA Study) for CEAP 2-5 subjects and one single arm active VLU Study with CEAP 6 subjects. Each study will be individually assessed and analyzed for the overall study objectives. The three primary endpoints in the Randomized Studies will be measured to compare VenaSeal vs. the treatment of ETA or surgical stripping on VenousTSQe and VenousTSQs (separately) at 30 days, and elimination of clinically relevant superficial truncal disease in the target vein at the time of index procedure. The primary endpoint of the VLU Study is time to ulcer healing and will be measured until healing has occurred through 12 months. Subjects randomized within the VenaSeal vs. Surgical Stripping Study will be followed through the 12 months visit. In this study, the elimination of clinically relevant superficial truncal disease in the target vein at the time of index procedure will be summarized between two treatment arms but there is no formal hypothesis to be tested. The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods used to analyze the study objectives. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report. All statistical analyses will be performed using Statistical Analysis System (SAS) software (version 9.2 or higher) or other widely accepted statistical or graphical software.

4. Introduction

4.1. Background

Venous Reflux Disease

Venous reflux disease (VRD) is a type of chronic venous disease (CVD) also known as venous insufficiency, a medical condition which affects the circulation of blood through the venous system of the lower extremities.

VRD of the lower extremities is a chronic and progressive disorder that is influenced by genetic and mechanical factors. It is believed to result from abnormal distensibility of the connective tissue present in the vein wall which ultimately results in venous dilatation and the failure of one-way valves present within the veins that direct the return of blood up the lower limb.[1] Incompetence of the valves and hypertrophy of the vein wall result in backflow, or venous reflux, and a pooling of the blood in the superficial veins. Reflux in the superficial venous system, commonly known as varicose veins, is estimated to affect 23% of all adults in the U.S.[2,3] The Framingham study (1988) found that VRD was twice as prevalent as coronary heart disease and five times as prevalent as Peripheral Arterial Disease (PAD), and that up to 90% with symptomatic venous reflux are untreated.[4] The more advanced stages of the disease affect approximately 5% of the population, with active ulcerative end stage disease present in about 1-2%.[5,6] Great Saphenous Vein (GSV) insufficiency is the most common manifestation of varicose veins, although small saphenous (SSV), accessory saphenous, and duplicate veins that travel in parallel with the great and small saphenous veins (SSV) may also be affected.[7]

CVD is considered a major socioeconomic burden throughout the world with a budgetary impact greater than that of arterial disease.[8] At least 63.9% of over 90,000 subjects in a Vein Consult Program, providing data from Europe, Latin America, the Middle East and the Far East, were diagnosed with CVD.[9] It was recently described that in Western Europe, 2% of the annual healthcare budget is spent on chronic venous conditions (900 million Euros). Venous ulcers, which could be prevented by early therapy, contribute to 2 million lost workdays annually in the US.[10,11]

Diagnosis and Classification of Disease Severity

Primary varicose veins initially develop in subcutaneous veins with diameters ≤ 3 mm and are at first accompanied by few signs of CVD.[12] As the disease progresses, patients with varicose veins develop one or more symptoms that might include heaviness, aching or throbbing pain in the lower legs, cramps, restless leg syndrome, pruritus (itchiness), fatigue, swelling, and tenderness along the varicosity.[13] Thrombophlebitis or bleeding from superficial varicose veins may be evident at diagnosis, as might the changes indicative of more advanced CVD such as edema, eczema, pigment changes, and ulcerations.[6,14,15] The skin changes occur due to sustained venous hypertension concomitant with CVD.[16]

To adequately manage and treat venous reflux, the patient's CVD must be accurately diagnosed and classified, with a focus on the underlying venous problem. Patients typically undergo non-invasive Duplex Ultrasound (DUS) scanning in accordance with guidelines for investigation of lower limb disease. DUS is considered the gold standard in diagnosis of VRD and is used in pre- and postoperative assessment as well as during therapy for minimally invasive procedures. The GSV, Anterior Accessory Saphenous Vein (AASV), Posterior Accessory Saphenous Vein (PASV), thigh extension, and the SSV are the main superficial conduits imaged and tested for possible reflux prior to therapy.

One of the most well-accepted methods to evaluate the clinical signs of VRD is the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification system.[2,6,17] The CEAP includes four categories of assessment: the clinical signs of the disease (C), the etiology or cause of the disease (E), the anatomy of the disease (A), and its underlying pathophysiology (P). Based upon these assessments, the severity of the disease can be classified. Stages range from CEAP 0 to CEAP 6. The clinical signs range from no visible signs of the disease to venous disease with multiple symptomology and active venous ulcerations.[12]

Treatment of VRD

Traditional surgical removal of the incompetent varicose veins was for many years considered a gold standard for the treatment of superficial venous reflux. Such an approach is generally achieved by surgical ligation and stripping of incompetent superficial truncal veins. This procedure may require use of general anesthesia and has been associated with significant perioperative morbidity including postoperative pain [18,19] and slow recovery to normal daily activities.[20]

Therapies are often combined for maximum treatment benefit. Sclerotherapy is a minimally invasive endovenous treatment option in which a sclerosing compound (foam or liquid) is delivered directly into the target vein. The injected compound produces endothelial damage and inflammation which lead to "sclerotic changes" in the vein wall and eventual fibrosis across the vein lumen.[21] Sclerotherapy is often used adjunctively with other primary treatments and is allowable in this study as described in section 10, study procedures. Disadvantages of sclerotherapy as a primary treatment include poor efficacy requiring multiple treatments and prolonged compression hose therapy following treatment.[22] General risks associated with sclerotherapy are similar to other endovenous therapies and include thrombophlebitis, localized phlebitis, hyperpigmentation, telangiectatic matting, and transient pain.[21, 22, 23, 24]

In response to the complications associated with the surgical treatment, minimally invasive procedures have been developed. Interventions such as endothermal ablation (ETA) are minimally invasive procedures and include endovenous laser ablation (EVLA) that uses laser or radiofrequency ablation (RFA) that uses radiofrequency heating to seal the vessel. Heat is applied in both the therapies to ablate the target vein via a different medium. The underlying goal for all thermal ablation procedures is to deliver sufficient thermal energy to the wall of the incompetent vein segment to coapt the vein wall and achieve occlusion, and fibrosis. RFA involves delivery of controlled radiofrequency energy through a generator which heats a segment of the catheter which is inserted into the diseased vein. A tumescent anesthetic is administered around the vein, the catheter is inserted, and the radiofrequency energy is delivered to occlude the vein. The heat causes the vein to contract and occlude. EVLA involves use of a laser catheter and is inserted into the venous system via percutaneous access using duplex ultrasound (DUS) guidance or by open venotomy. A tumescent anesthetic is also administered around the vein, laser energy is applied to the inside of the vein and the vein is sealed. Despite EVLA and RFA being minimally invasive, there are

disadvantages and risks with ETA, including hematoma, thrombophlebitis, venous thrombosis, vessel perforation, skin burns, paresthesia of the leg, the need for multiple needle sticks to apply large volumes (150-1000 cc) of perivenous anesthetic (i.e., tumescent anesthesia), or injury to the sural or saphenous nerve.[25] Tumescent anesthesia is painful during administration and can lead to ecchymosis and longer recovery time.

The VenaSeal™ closure system was developed as a non-thermal, non-tumescent and non-sclerosant (NTNTNS) alternative to other available treatment options, specifically thermal and tumescent options which require the usage of tumescent anesthesia and involve risk of thermal injury.[25] The VenaSeal™ system uses a medical grade adhesive to eliminate the primary source of reflux by coapting the vein walls. Closure of the insufficient vein is accomplished through polymerization of a cyanoacrylate-based adhesive delivered via a catheter, and the resultant acute coaptation of blood flow is followed by eventual encapsulation of the blockage.

Summary of VenaSeal™ Closure System Clinical Studies

Feasibility Study

The Feasibility Study was a prospective, single center study performed in the Dominican Republic to assess safety and VenaSeal™ effectiveness to treat VRD in the GSV. Effectiveness results of the Feasibility Study indicated a 94.7% closure rate at 6 months following the index procedure. Subjects were followed for 36 months in total. There were 4 Serious Adverse Events (SAEs) reported in 3 subjects, with 1 of the 4 determined to be related to the study device or study procedure. An additional 24 Adverse Events (AEs) were reported in 17 subjects. Finally, 1 Deep Vein Thrombosis (DVT) was observed at 31 months post-treatment in a hypercoagulable subject (unknown device relationship, not related to the procedure).

eSCOPE Post-Market Study

The eSCOPE Post-Market Study was a multicenter, prospective, single arm study conducted in Europe designed to record the clinical outcomes of the CE-marked VenaSeal™ closure system for its approved indications. The primary objective was to assess the role of the VenaSeal™ system in closure of incompetent GSVs in a routine clinical setting. Effectiveness and safety (AEs) were compared to appropriate literature reports as per individual study protocols to determine if the results of the treatment of reflux disease with the VenaSeal™ system were consistent with or better than the expectations of the medical community for alternative treatments, specifically endovenous laser thermal ablation and RFA. Effectiveness results indicated a 91.4% closure rate at 6 months, declining to 88.5% closure at 36 months. At 6 months, safety analysis observed 32 AEs, one of which was an unrelated serious adverse event.

VeClose IDE Pivotal Study

The VeClose Study was a randomized, prospective, multicenter study conducted to demonstrate safety and effectiveness of the VenaSeal™ system for the treatment of lower-extremity truncal reflux compared to RFA performed using the ClosureFast™ System. This study was conducted in the United States under Investigational Device Exemption (IDE) G120204, data from the study was used to support a premarket approval (PMA) application. The PMA Application was approved by the FDA on February 20, 2015.

The study's primary effectiveness endpoint was at 3 months. The primary safety assessment was performed at 1 month. The study was originally completed on April 10, 2017. The original results of the study, including 3-year follow-up data are summarized below.

A total of 242 subjects from 10 US clinical sites were treated in the study. There were 20 subjects treated and analyzed in the roll-in cohort and 222 subjects in the randomized cohorts (108 in VenaSeal™ system and 114 in RFA). The overall mean age was 50 years (range 25 – 70) and the study population was consistent with the known female predominance of venous disease, with primarily female subjects (80%). The majority of subjects (56.6%) entered the study with venous disease in the study limb classified as CEAP 2. Aching and pain were the 2 most frequently reported dominant symptoms, with over 25% of subjects reporting these symptoms. There were no statistically significant differences in the demographics or baseline parameters between the randomized groups (VenaSeal™ system and RFA).

Effectiveness was measured as vein closure at 3, 12, 24 and 36 months. At 3 months, the closure rate observed was 99.0% for the cyanoacrylate group and 96% for the RFA group decreasing to 94.4% by 36 months for the cyanoacrylate group and 91.9% for the RFA group.[26] There were no statistically significant differences in rates of any individual AEs between the randomized VenaSeal™ system group and the RFA group through 36 months. For both groups, the majority of subjects reported no AEs, and of those who reported AEs, the majority had only one event. A total of 156 AEs were reported in 100 subjects; 78 AEs in 47 VenaSeal™ system subjects, 15 AEs in 11 roll-in subjects, and 63 AEs in 42 RFA subjects. A total of 15 serious adverse events (SAEs) were reported in 12 subjects (5 VenaSeal™ system, 1 roll-in, and 6 RFA). All were assessed as unrelated to the study device or study procedure.[26,27,28,29]

There was one report of death (due to liver cancer) in a VenaSeal™ system subject. The liver cancer death at Day 1098 post-procedure was assessed as unrelated to the study device or study procedure. There was one report of deep venous thrombosis (DVT) in the non-index limb in an RFA subject. There were no reports of Pulmonary Embolism (PE), no reports of allergic reactions to the VenaSeal™ adhesive (cyanoacrylate), and no reports of Unanticipated Adverse Device Effects (UADEs).

VeClose Five-Year Follow-up Extension Study

The VeClose Five-Year Follow-up Extension study was conducted to gain additional follow-up data from the patients enrolled in the VeClose IDE pivotal study described above. Patients treated in both the experimental and control study arms as well as in the roll-in cohort were assessed for a 60-month follow-up visit. The study was conducted under a separate protocol and no further intervention occurred under this protocol. A total of 89 subjects completed the 60-month visit, 9 subjects were from the roll-in cohort and 80 subjects from randomization cohort (47 subjects in VenaSeal™ system and 33 subjects in RFA). 53 subjects treated with the VenaSeal™ system (subjects enrolled in VenaSeal™ system + roll-in subjects) maintained a closure rate of 94.6% at 60 months. The closure rate for 33 subjects treated with RFA was 100%. Kaplan-Meier freedom-from-recanalization analysis demonstrated non-inferiority of the VenaSeal™ system compared to the RFA group at a significance level of 0.025 (non-inferiority based on one-sided 97.5% confidence interval with lower limit = -3.5%, and margin of -10%), through the 60-month follow-up period (91.4% vs. 85.2%, respectively). These rates remained unchanged from the 36-month follow-up visit, indicating that no new GSV failures occurred between the 36- and 60-month visits in either group. No SAE, PE, DVT or treatment limb AEs were reported in both the VenaSeal™ system cohort and the RFA cohort between 36-month and 60-month follow-up.[30]

WAVES

In addition to the above industry-initiated studies, the Lake Washington Vascular VenaSeal™ Post-Market Evaluation (WAVES) study was a single-center multiple-investigator, single-arm prospective study investigating the use of the VenaSeal™ system in patients with symptomatic VRD. The study assessed the use of the VenaSeal™ system in GSVs (n=48), SSVs (n=8), and accessory saphenous veins (n=14).[31] Diseased veins of up to 20 mm diameter were included. The WAVES protocol did not allow adjunctive tributary treatment at the time of the index procedure which were staged at 3 months post-index procedure.

There were 70 veins treated in 50 subjects. All primary target veins (48 GSV, 14 ASV, and 8 SSV) showed 100% closure using DUS at 7 days and 1 month. Complete closure at 3 months was achieved in 70 (99%) of the treated veins. By 3 months, the revised Venous Clinical Severity Score (rVCSS) (6.5 ± 2.4 at baseline to 1.8 ± 1.4 at 1 month and 3 month; $p<0.001$), Aberdeen Varicose Vein Questionnaire (AVVQ) (17.3 ± 7.9 at baseline to 8.9 ± 6.6 at 1 month and 6.5 ±7.2 at 3 month; $p<0.001$), and the EQ VAS (84 ± 12 at baseline to 88.3 ± 8.7 at 1 month and 88.6 ± 10.6 at 3 month; $p = 0.002$) all showed statistical improvement between baseline and 1 month, and baseline and 3 month visits. The percentage of patients who required adjunctive treatments at three months was lower than had been predicted by the treating physicians (65% versus 96%, p=.0002).[32] Procedural pain was mild with a Nominal Pain Rating (NPR) of 2.2 ± 1.8, and the mean time to return to work and normal activities was 0.2 ± 1.1 and 2.4 ± 4.1 days, respectively.

Phlebitis was the most common AE, occurring in the treatment area or side branches in 10 patients (20%), but resolving in all but one subject (2%) by one month. One patient developed body hives within the first week of the procedure which was resolved following antihistamine and steroid treatment, this was said to be consistent with a cyanoacrylate allergy. There were no DVTs or other SAEs. One patient had a thrombus extension at the seven-day DUS which was no longer evident at the one-month DUS. Between the 1-month and 3-month visits, there was one AE, knee bursitis in the treatment limb which was determined as unrelated to the procedure.[32]

4.2. Purpose

The purpose of the VENASEAL SPECTRUM study is to evaluate the patient's experience and clinical improvement after treatment with the VenaSeal™ system compared to Standard of Care (SoC) treatments, surgical stripping or ETA, in the treatment of symptomatic superficial venous disease (CEAP 2-5). Patient-centered outcomes, vein closure, ability to return to work, and clinical improvement will be measured after treatment of symptomatic venous reflux in the superficial truncal veins by the VenaSeal™ system or the comparator treatments. Additionally, in a separate single-arm study, CEAP 6 patients with at least one active venous leg ulcer will be enrolled, treated with the VenaSeal™ system and evaluated for wound healing. This study will complement the available clinical evidence for the VenaSeal™ system.

There will be approximately 500 subjects enrolled in the VenaSeal Spectrum Study. Approximately 375 subjects will be enrolled in CEAP clinical classifications 2-5 in the Randomized Studies (108 subjects in VenaSeal vs. Surgical Stripping Study and about 264 subjects in VenaSeal vs. ETA Study), and up to 125 CEAP 6 subjects with VLUs will be treated with the VenaSeal™ system. Enrollment of the VenaSeal vs. Surgical Stripping Study was closed on 22-Feb-2022. All subjects participating in the VenaSeal vs ETA Study or in the VLU Study (CEAP 2-6) will be followed up to 60 months post-index procedure, all subjects participating in the VenaSeal vs. Surgical Stripping Study will be followed up to 12 months post-index procedure.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objectives

For the CEAP 2-5 Randomized Studies, the primary objectives are to compare the VenaSeal™ system to surgical stripping and ETA regarding patient experience and satisfaction, through a validated, patient-centered 2-part venous treatment satisfaction questionnaire (VenousTSQ-early [VenousTSQe] and

VenousTSQ-status [VenousTSQs]) at 30 days, and the ability to achieve elimination of clinically relevant superficial truncal disease in the target veins at the index procedure.

For the VLU Study, the primary objective is to evaluate time to ulcer healing through 12 months.

5.1.2. Secondary Objectives

The key secondary objectives are to compare the VenaSeal™ system to surgical stripping and ETA in achieving the anatomical closure of superficial truncal veins at 6 months, and the ability to return to work post-index procedure.

For all subjects, the secondary objective of the study is to evaluate the VenaSeal™ system in the treatment of symptomatic venous reflux in the superficial truncal veins. Specific areas of analysis include: effectiveness, safety, healthcare utilization, patient experience, and treating physician experience.

In addition, secondary objectives in the VLU Study include ulcer healing rate, ulcer recurrence, and ulcer-free time.

5.2. Endpoints

5.2.1 Primary Endpoints

The CEAP 2-5 Randomized Studies have three primary endpoints comparing the VenaSeal™ system to surgical stripping or ETA:

1. Peri-procedural patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days.
2. Patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days.
3. Elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure as measured by the percentage of target vein length successfully treated.

The Primary endpoint for the VLU Study is time to ulcer healing, calculated through healing confirmation and verified by an independent core laboratory through 12 months.

5.2.2 Key Secondary Endpoints

Data supporting the following endpoints will be collected for both the Randomized Studies as well as the VLU Study. The following endpoints will be compared for the Randomized Studies and will be evaluated for the VenaSeal™ system for the VLU Study.

1. Anatomic closure of the primary target superficial truncal vein at 6 months, defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm after VenaSeal™ system and ETA procedures, or the absence of refluxing or residual primary target vein after surgical stripping procedures.
2. Time to return to work as reported by the patient.

5.2.3 Secondary Endpoints

Data supporting the following endpoints will be collected for both the CEAP 2-5 Randomized Studies as well as the VLU Study. When appropriate, data will be evaluated for the CEAP 2-5 Randomized Studies to compare the VenaSeal™ system to surgical stripping or ETA. Data may also be pooled for all VenaSeal™ system subjects from the CEAP 2-5 Randomized Studies and VLU Study as appropriate. The surgical stripping data will be collected up to the 12 months' time point.

Effectiveness secondary endpoints

1. Anatomic closure of primary target vein at 30 days, and 12, 24, 36, 48 and 60 months:
   - For subjects treated with the VenaSeal™ system or ETA it is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.
   - For subjects treated with surgical stripping this is defined as absence of refluxing or residual vein and it will be collected at 30 days and 12 months only.
2. Anatomic closure of target vein at 30 days, and 6, 12, 24, 36, 48 and 60 months:
   - For subjects treated with the VenaSeal™ system or ETA this is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.
   - For subjects treated with surgical stripping this is defined as absence of refluxing or residual vein and it will be collected at 30 days, 6 and 12 months only.
3. Technical success of each target vein immediately post-index procedure:
   - For subjects treated with the VenaSeal™ system or ETA this is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.
   - For subjects treated with surgical stripping this is defined as absence of refluxing or residual vein.
4. Reintervention of any target vein (including primary target vein) through 60 months, assessed at each follow-up visit (through 12 months for subjects enrolled in the VenaSeal vs. Surgical Stripping Study).
5. Time to reintervention of any target vein (including primary target vein) through 60 months, as measured by the time between the index procedure and the first reintervention procedure (through 12 months for subjects enrolled in the VenaSeal vs. Surgical Stripping Study).

Safety secondary endpoints

6. Adverse events (AEs) occurring in the target limb, evaluated from index procedure through 12 months:
   - Hypersensitivity to VenaSeal™ adhesive
   - Phlebitis
   - Granuloma
   - Endovenous glue induced thrombosis (EGIT) or endovenous heat induced thrombosis (EHIT)
   - Symptomatic deep vein thrombosis (DVT) events
7. Additional events evaluated through 60 months (through 12 months for subjects enrolled in the VenaSeal vs. Surgical Stripping Study):
   - Symptomatic pulmonary embolism (PE)
   - Serious adverse events (SAEs)

Healthcare utilization secondary endpoints

8. Number and type of adjunctive treatments conducted through 12 months post-index procedure.
9. Healthcare utilization related to the target limb VRD, as determined by the number of healthcare visits conducted, and other health-related resources utilized (e.g., home healthcare services) between study visits through 60 months (30 days, 6 and 12 months only for subjects enrolled within the VenaSeal vs. Surgical Stripping Study).
10. Procedures, tests and treatment of AEs related to the treatment modality or index procedure.
11. VLU Study: Healthcare utilization and routine wound care treatments between study visits through 60 months.

Patient Experience secondary endpoints

12. Time to return to normal activities as reported by the patients.
13. Intra-procedural and post-procedural pain at the index procedure, and 7 days and 30 days as reported by the patient using the numeric rating scale (NRS) with a scale of 0-10.
14. Change in venous disease symptoms at 7 and 30 days, and at 6, 12, 24, 36, 48, and 60 months compared to baseline (7 days, 30 days, 6 and 12 months only for subjects enrolled in the VenaSeal vs. Surgical Stripping Study), as measured by the revised Venous Clinical Severity Score (rVCSS) and subject self-reporting.

15. Change in AVVQ score at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for subjects enrolled in the VenaSeal vs. Surgical Stripping Study) compared to baseline.
16. Change in EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) at 30 days, and 6, 12, 24, 36, 48 and 60 months (30 days, 6 and 12 months only for subjects enrolled in the VenaSeal vs. Surgical Stripping Study) compared to baseline.
17. Change in the 36-Item Short Form Health Survey (SF-36) reported by the patient at 30 days, and 6 and 12 months compared to baseline.
18. Change in the Venous Dependent Quality of Life (VenousDQoL) reported by the patient at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for subjects enrolled in the VenaSeal vs. Surgical Stripping Study) compared to baseline.

Provider Experience secondary endpoint

19. Provider experience will be assessed post-index procedure, evaluating overall satisfaction with the procedure.

VLU Study:

The primary endpoint of the VLU Study is referenced in section 5.2.1, Primary endpoints.

The following ulcer-specific effectiveness endpoints will be evaluated:

20. Ulcer healing rate, as measured by the percentage of the ulcer area healed per given time period, according to an independent core laboratory through 24 months or until ulcer healing has been confirmed.
21. Ulcer recurrence on the target limb, assessed at all follow-up timepoints following ulcer healing through 60 months.
22. Ulcer-free time, calculated as days between initial ulcer healing and first ulcer recurrence, as applicable, through 60 months.

In addition, the primary endpoints and any other applicable endpoints of the Randomized Studies will be also assessed for the VLU Study:

23. Peri-procedural patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days.
24. Patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days.
25. Elimination of clinically relevant superficial truncal disease in target vein at the time of index procedure as measured by the percentage of target veins successfully treated.

6. Study Design

The study design is a global, post-market, prospective, multi-center, randomized-controlled study of patients with symptomatic superficial venous disease, with a single-arm embedded ulcer group. The study is designed with two Randomized Studies (VenaSeal vs. Surgical Stripping Study and VenaSeal vs. ETA Study) for CEAP 2-5 subjects and one single arm active VLU Study for CEAP 6 subjects. Each study will be individually assessed and analyzed for the overall study objectives. The two Randomized Studies (VenaSeal vs. Surgical Stripping Study and VenaSeal vs. ETA Study) will not be blinded due to the significant differences between the treatments and after care which would prevent the patient from being able to be blinded. For example: surgical stripping subjects will undergo a surgical procedure with several possible types of anesthesia including general anesthesia, whereas VenaSeal and ETA subjects will undergo a minimally invasive intervention with limitations in allowed anesthesia; these different anesthesia types require significantly different post-treatment care. In addition, due to the post-market nature of the study, where allowable within regions, patient insurance will be utilized to cover the cost of the procedure, however each procedure may result in differing financial impacts to the patient. Due to these inherently different aspects, blinding of treating physicians or patients would not be possible, and patients could potentially be put at higher risk due to blinding.

There will be approximately 500 subjects enrolled in the VenaSeal Spectrum Study. Approximately 375 subjects will be enrolled in CEAP clinical classifications 2-5 in the Randomized Studies (108 subjects in VenaSeal vs. Surgical Stripping Study and about 264 subjects in VenaSeal vs. ETA Study), and up to 125 CEAP 6 subjects with VLUs will be treated with the VenaSeal™ system.

On 22-Feb-2022, enrollment closed to participating VenaSeal vs. Surgical Stripping Study sites within the VenaSeal Spectrum clinical study. Subjects randomized in this study will be followed up to and including the 12 months visit.

Enrollment will take place at up to 40 sites globally. A list of participating investigational sites which includes the name, position, emergency contact details and address of the investigators responsible for conducting the study will be available under a separate cover (including additional regions that may be added to the study).

Currently, ETA and surgical stripping are the most common health insurance-covered treatments for VRD in a global setting. ETA is standard of care both in the United States and outside of the United States. Surgical stripping is not standard of care in the United States and is practiced as primary treatment outside of the United States. Hence, in the United States, sites will only participate in VenaSeal vs. ETA Study and/or the VLU Study. Outside of the United States, sites will participate in either the VenaSeal vs. ETA Study or the VenaSeal vs. Surgical Stripping Study, and/or the VLU Study. Beginning with version 4.0 of

the VenaSeal Spectrum CIP, no new sites will be activated for participation in the VenaSeal vs. Surgical Stripping Study and no additional VenaSeal vs. surgical stripping subjects will be enrolled. Sites in all geographies may participate in the VLU and VenaSeal vs. ETA Study. Site designation for all studies will be indicated in the Site Selection Letter provided by Medtronic.

To avoid introduction of bias to the study results due to disproportionate enrollment, enrollment at any individual site shall not exceed 20% of any single study (approximately 50 subjects for the Randomized Studies and 25 subjects for the VLU Study, excluding screen failures) of the total sample size. It is expected that sites enroll a minimum of 10 subjects per individual study the site is participating in.

The study methods include the following measures to minimize potential sources of bias:

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, SAEs, target limb AEs including hypersensitivity, phlebitis, granuloma, and EGIT or EHIT. Safety results for these events will be reported based on CEC adjudication.
- An ulcer core laboratory will evaluate all CEAP 6 subjects who are enrolled into the study with active VLUs. VLU size measurements will be based on ulcer core laboratory evaluation as well as final confirmation of ulcer healing.
- Study monitors will verify subject data and ensure compliance with the clinical investigation plan and other study requirements per the monitoring plan.
- Statistical analysis plan (SAP) will be developed prior to the analysis of the objectives.
- To avoid bias during randomization: Oracle Clinical will be used for randomization of subjects, stratified by study site and CEAP classification (2004).

6.1. Duration

It is anticipated that enrollment will take approximately 36 months following enrollment of the first subject. The estimated study duration is approximately 8 years, including up to 60-month follow-up post-procedure and excluding the time required for preparing the final report. The expected duration of each subject's participation is up to 60 months after the index procedure, apart from subjects who were enrolled in the VenaSeal vs. Surgical Stripping Study. The latter will be followed through 12-months only.

Data will be recorded in the Case Report Form (CRF) at screening, baseline, index procedure (day 0), and during follow-up at 7 days (± 2 days), 30 days (± 7 days), 6 months (± 4 weeks), 12 months (± 8 weeks), 24 months (± 8 weeks), 36 months (± 8 weeks), 48 months (± 8 weeks) and 60 months (± 8 weeks). Additional routine care visits can be conducted to accommodate adjunctive procedures 3 or more months following the index procedure (data for adjunctive procedures will be collected through 60 months), per the treating physician's discretion; these will not be considered study visits.

Data of subjects who were enrolled in the VenaSeal vs. Surgical Stripping Study will be recorded in the CRF at screening, baseline, index procedure (day 0), and during follow up at 7 days (± 2 days), 30 days (± 7 days), 6 months (± 4 weeks), and 12 months (± 8 weeks).

CEAP 6 subjects will have additional study visits until healing verification and data will be recorded in the CRFs at: 2 months (± 7 days), 3 months (± 7 days), 4 months (± 7 days), 5 months (± 7 days), 8 months (± 2 weeks), 10 months (± 2 weeks). If the healing has not occurred by 12 months, subjects will continue to follow standard wound care and remaining study visits. Subjects will come in for ulcer healing verification visit up to 24 months, after which no core laboratory ulcer assessment for wound healing will be required.

6.2. Rationale

Currently, ETA and surgical stripping (outside of the US) are the most common treatments of VRD. This study is being conducted to evaluate the patient's experience and clinical improvement after treatment with the VenaSeal™ system compared to standard of care treatments, surgical stripping or ETA, in the treatment of symptomatic superficial venous disease (CEAP 2-5). Patient-centered outcomes, vein closure, ability to return to work and clinical improvement will be measured after treatment of symptomatic venous reflux in the superficial truncal veins by the VenaSeal™ system or the comparator treatments. In a separate single-arm VLU Study, CEAP 6 patients with at least one active venous leg ulcer will be enrolled and treated with the VenaSeal™ system and evaluated for wound healing.

By collecting additional data regarding the provider experience, patient experience, safety, quality of life, patient satisfaction, ability to return to normal activities, procedural experience and healthcare resource utilization, this study will provide foundational evidence for further characterizing the VenaSeal™ system. In addition, this study represents the first VenaSeal™ system study focusing on the active VLU (CEAP 6) population, evaluating time to ulcer healing, ulcer healing rate, ulcer recurrence, and ulcer-free time.

The justification of the study design is based on a clinical evaluation and is aligned with the risk assessment done for the study, given the post market nature of all the devices and procedures involved.

The decision of closure of the VenaSeal vs. Surgical Stripping Study enrollment was made due to significant delays and challenges recruiting sites and subjects during the global COVID-19 pandemic. The subjects enrolled in VenaSeal vs. Surgical Stripping Study will still be followed through 12 months to ensure follow-up through the first year following procedure.

The primary endpoint for the VLU study for time to ulcer healing is updated from 24 months to 12 months to align with landmark clinical trials in superficial venous space.

The hypothesis test was removed for the primary endpoint of elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure for the VenaSeal vs. Surgical Stripping Study as the endpoint is no longer powered with the reduced sample size. However, results will still be summarized between study arms.

Subjects may also complete 48 and 60 months visit remotely per physician's discretion if subjects cannot return to the site for follow-up. The long-term follow-up visits, 48 and 60 months may have higher attrition rate. The remote visit is permitted in the study for 48 and 60 months to keep the attrition rate minimal and be able to collect long term study data as much as possible.

Data for adjunctive therapies and additional treatments will be collected till 60 months to ensure accuracy of data on healthcare utilization.

Data on perforating veins for CEAP 4b or 5 on the target limb are collected from 3 months through study end to perform an accurate healthcare utilization analysis.

The exclusion criterion on COVID-19 has been updated to reflect the current understanding and guidelines.

7. Product Description

The primary product in the study is the VenaSeal™ closure system and is described below. The use of comparator products that will be included in ETA are per the study site's standard of care or the treating physician's discretion. The comparator products are not described in this protocol and the current version of the Instructions for Use (IFU) available at the time of the study procedure with the appropriate product should be utilized. The surgical stripping procedure should be performed per treating physician's standard of care.

7.1. General

The VenaSeal™ system is a medical device kit consisting of delivery tools and proprietary VenaSeal™ adhesive used to treat venous reflux insufficiency in lower-extremity superficial truncal veins. The VenaSeal™ system offers an outpatient treatment option for permanently occluding superficial truncal veins.

The VenaSeal™ system includes one 5 cc vial of VenaSeal™ adhesive and the VenaSeal™ Delivery System components.

Figure 1: VenaSeal™ adhesive

Figure 2: VenaSeal™ Components in a Tray

The VenaSeal™ Delivery System consists of 7 delivery tools used to facilitate endovascular placement and delivery of VenaSeal™ adhesive in the target vessel during the delivery procedure:

- Introducer
- Dilator
- Catheter
- Dispenser gun
- Dispenser tips
- 3 cc syringes
- Guidewire

All materials that may contact tissues and/or body fluids are presented in the **Table 3**:

Table 3: Materials in contact with tissues and/or body fluids

VenaSeal™ system device component	Materials
VenaSeal adhesive	• Proprietary Cyanoacrylate adhesive
Introducer	• Extrusion: Polyethylene homopolymer, Filler, Pigment, Color Concentrate High Density Polyethylene
Dilator	• High Density Polyethylene Extrusion: Polyethylene hexene copolymer, Filler, Color Concentrate

VenaSeal™ system device component	Materials
Catheter	• Extrusion: Polytetrafluoroethylene Extruded • Extrusion: Polytetrafluoroethylene Extruded Unfilled, Natural • Hub: High Density Polyethylene
.035" Guide Wire	• Core: Stainless Steel Medical Grade • Coating: Polytetrafluoroethylene
3mL Monoject Luer Lock Syringe	• Barrel: Polypropylene Copolymer • Plunger Tip: SSBR Rubber Compound (Silicon-free rubber)
14 Gauge SS Dispensing Tip	• Hub: Polypropylene, proprietary stabilizers/colorant • Cannula: Stainless Steel • Adhesive: UV Adhesive
Captive J-Straightener	• Polypropylene, Pantone 264-U Purple

All tools are provided sterile and are intended for single patient use. Designs are based on applicable standards for similar devices.

Current VenaSeal™ System model numbers information is listed below in **Table 4**:

Table 4: Current VenaSeal™ System model numbers

Model Number	Product (Manufacturer)	Investigational or Market-released
SP 101	VenaSeal™ System (Medtronic Inc.)	Market-released
VS 402	VenaSeal™ System (Medtronic Inc.)	Market-released
VS 403	VenaSeal™ System (Medtronic Inc.)	Market-released
VS 404	VenaSeal™ System (Medtronic Inc.)	Market-released

In the event that additional model numbers become available during the study, an updated model number list will be made available under a separate cover.

7.2. Manufacturer

The VenaSeal™ closure system is manufactured in accordance with standard procedures and specifications under 21 Code of Federal (CFR) 820 and International Organization for Standardization (ISO) 13485:2016. The legal manufacturer is listed below:

Medtronic Inc.
710 Medtronic Parkway
Minneapolis, Minnesota 55432 USA

7.3. Packaging

The study will be conducted in geographies where the VenaSeal™ closure system is commercially available. The packaging and labeling are in accordance with local regulations and available in local languages as applicable. The VenaSeal™ system is delivered in a sterile package for single use only.

7.4. Intended Population

The VenaSeal™ closure system will be used according to the IFU criteria as applicable per region. The indications listed here are at time of protocol finalization. Please refer to the respective IFU for current and applicable indications.

The VenaSeal™ system achieved European Conformity (CE) mark status in September 2011, Food and Drug Administration (FDA) approval in the United States in February 2015, and approval in South Korea in October 2016.

United States (U.S.) Indication (VS-402, VS-404): The VenaSeal™ system is indicated for use in the permanent closure of lower extremity superficial truncal veins, such as the GSV, through endovascular embolization with coaptation. The VenaSeal™ system is intended for use in adults with clinically symptomatic venous reflux as diagnosed by DUS.

Outside of the United States (OUS) Indication (VS-403, SP-101): The VenaSeal™ system is intended for the permanent, complete, endovascular adhesive closure of the GSV and associated varicosities in the treatment of VRD.

South Korea Indication (SP-101): The VenaSeal™ system is intended for use in patients with venous reflux disease as diagnosed by duplex ultrasound (DUS). The VenaSeal™ system is indicated for use in the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV), through endovascular adhesive closure.

If any additional regions are added to the study, the current IFU applicable to the region should be followed.

The use of the VenaSeal™ system is contraindicated when any of the following conditions exist:

- Previous hypersensitivity reactions to the VenaSeal™ adhesive or cyanoacrylates
- Acute superficial thrombophlebitis
- Thrombophlebitis migrans
- Acute sepsis.

7.5. Equipment

Any test equipment critical to be used for assessing endpoints (e.g., DUS) will be maintained/calibrated and documented according to the site's standard protocol. The maintenance and calibration report should be made available to monitors upon request.

7.6. Product Use

The device should be used within the intended use described in the IFU for subjects who meet the eligibility criteria for the study. The VenaSeal™ closure system will be obtained by the study sites according to their standard procedures for commercial products. The site must store devices as labelled. The identification number of the VenaSeal™ system used for enrolled subjects will be captured in the study database.

7.7. Product Training Materials

Treating physician training for the study products is to be completed per local regulations prior to study participation. Additional, study-driven training is not required as the products used in the study are commercially available. However, all treating physicians are required to have minimum experience with the study product as explained in section 8.1.

7.8. Product Accountability

Commercially available product supply will be managed in a manner consistent with other market-released products. All products used in this study will be market released in the geographies they are used. Device Traceability may be required per local laws and regulations. If there are additional local requirements related to the VenaSeal™ system beyond what is collected by Medtronic on the CRF, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be

collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the study, lot or batch number). Full device tracking as required by ISO 14155:2020 will not be performed due to the post-market nature of the study.

8. Study Site Requirements

8.1. Investigator/Investigation Site Selection

All investigators managing the subject's superficial venous disease must be qualified practitioners and experienced in the diagnosis and treatment of subjects with superficial venous disease. All treating physicians must be experienced and/or trained in the handling of the VenaSeal™ system if they are delegated to treating VenaSeal subjects and, depending on the randomized study they will participate in, either in a standard of care ETA treatment modality or the surgical stripping procedure. In addition, only a physician is allowed to carry out the index procedure, regardless of local laws governing endovenous procedures. The investigator's experience with superficial venous treatment will be documented on a separate physician experience form prior to the individual's activation for the study.

Additional, qualifying treating physicians may be added to a site and activated at any point in the study, following meeting all the above requirements, all appropriate training and study team approval.

The role of the Principal Investigator (PI) is to implement and manage the day-to-day conduct of the clinical investigation as well as to ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The Principal Investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation.
- Be experienced in the field of application and training in the use of the VenaSeal™ system.
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results.
- Be able to demonstrate that the proposed investigational study site has:
    - The required number of eligible subjects needed within the recruitment period.
    - One or more qualified investigators, a qualified investigational study site team, and adequate facilities for the foreseen duration of the clinical investigation.

Study site personnel training will be completed and documented prior to participation in this study.

8.2. Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the current version of the clinical investigation plan (CIP), relevant standards and regulations (as needed), informed consent, and data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before being activated by Medtronic and contributing to the study. The PI and study site personnel who are trained to the study protocol and all relevant documents can also train other study site personnel in accordance to their role as needed. All participating study site staff must be delegated by the PI to perform study related activities. Medtronic will provide each study site with documentation of study site readiness. PI, Sub-Investigators and research coordinators participating in the study will also receive a Site Activation Letter; this letter must be received prior to performing study related activities. DUS technicians will not receive a Site Activation Letter but are required to provide training documentation and listing on the site's delegation task list prior to commencing study related activities.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- Institutional Review Board (IRB)/Ethics Committee (EC)/Competent Authority (CA) approval (and voting list, as required by local law) of the current version of the CIP and Informed Consent Form (ICF).
- Regulatory Authority approval or notification (as required per local law).
- Fully executed Clinical Trial Agreement (CTA).
- Complete site documentation including but not limited to Financial Disclosure, CV of Investigators and key members of investigation study site team, Delegated Task List, and Training Record.

Due to the COVID-19 global pandemic, a COVID-19 site activation assessment shall be completed with the site in order to assess a site's readiness to be activated, and to ensure the protection of subjects in accordance to the study CIP. The assessment consists of a checklist that provides recommended criteria to be assessed and to be verified prior to resuming study-related activities. Consideration should be made to minimize risk to subjects due to COVID-19 including all study-specific non-standard of care activities and post-procedural care (i.e., location, travel, etc.). Sites should evaluate if a subject is suitable for enrollment based on their individual situation including the applicable IRB/EC, local, and country guidance to reduce associated COVID-19 risks and to maintain adherence to the CIP including index procedures, subject follow-up visits, medical assessments, and imaging compliance. Sites should also be able to support either on-site or remote monitoring prior to activation. If, during the conduct of the trial, a site's COVID-19 impact changes, Medtronic reserves the right to re-assess the site's ability to continue with subject enrollment and follow-up at any point following site activation.

8.3. Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study under supervision of the PI, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.
- Technical support during the procedure under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites.
- Monitoring and auditing activities.

Representatives from Medtronic may provide technical support during the procedures to the treating physicians and study site staff relative to the use of the VenaSeal™ system and in relation to the collection of data during the index procedure. This will not bias the data integrity in any way. Initial technical support may be provided by Medtronic during the first few VenaSeal procedures at a site to ensure that the technique is carried out consistently according to the device's IFU by all treating physicians. In addition, the technical support will also have the purpose to ensure that the necessary study datapoints are considered and collected for all procedures that are part of this study. This is expected to lead to high quality data that is consistently collected among all global sites. Technical support for the comparator therapy procedures will only be provided in relation to data collection, as participating sites will have more experience with comparator therapies being SoC.

9. Selection of Subjects

9.1. Study Population

Patients 18 years of age or older requiring treatment of symptomatic venous reflux within the superficial truncal veins may be considered for this study if they meet all of the inclusion and none of the exclusion criteria outlined in this clinical investigation plan. Patients with CEAP 2-5 will be screened for the Randomized Study; VenaSeal vs. ETA Study. As of February 22, 2022, enrollment closed in the VenaSeal vs. Surgical Stripping Study. Patients with CEAP 6 will be screened for the active VLU Study. Due to the post-market nature of the study, the investigational population is almost identical to the device's target population except for the exclusion of the non-ambulatory patients.

9.2. Subject Screening and Enrollment

Patients with symptomatic venous reflux (2004 CEAP 2-6) in the superficial truncal veins (GSV, SSV, accessory saphenous vein) will be screened for possible inclusion in the study. Patients with CEAP 2-5 will

be screened for the Randomized Studies. CEAP 6 patients with symptomatic reflux in the superficial truncal veins eligible for vein closure using the VenaSeal™ system will be screened only at designated VLU sites for the VLU Study; these subjects will not be randomized.

During the study, Medtronic may limit enrollments of specific CEAP classifications, if needed to achieve a balanced distribution across clinical severity subgroups.

A combination of medical records, history and physical examinations, as well as standard of care DUS examination may be utilized for screening and identification of potential target veins.

Patients who meet all eligibility criteria and sign and date the ICF will be considered 'screened' from the point they have signed and dated the ICF. Information needed to assess eligibility will, in most cases, already be captured via routine care prior to consent. If the routine diagnostic DUS is older than 6 months, this will need to be redone in order to verify eligibility. In the instance that a screened subject no longer meets all eligibility criteria, the screened patient will be considered a 'screen failure'.

All patients that will be identified for the potential screening in the study will be added to the 'Pre-Screening Log'. In the 'Pre-Screening Log', sites will document the general reason for why a patient was not consented in the pre-specified categories. All subjects that sign and date the informed consent will be added to the Oracle database and hence there will be no need to maintain an additional 'Subject Screening Log' unless it is the site's preference to do so. All subjects that are enrolled will be documented in the 'Subject Identification and Enrollment Log' (subject name, date of birth, subject identification number, enrollment date and randomization arm as applicable), which will not be collected by Medtronic but should be available for monitor review while on site.

CEAP 2-5 Subjects

After the patient has signed the ICF, met all of the inclusion and none of the exclusion criteria, the CEAP 2-5 subjects will be randomized to one of the treatment arms, refer to section 10.4, Randomization and Treatment Assignment (CEAP 2-5) for more details. CEAP 2-5 subjects will be considered 'enrolled' from the moment of randomization.

CEAP 6 Subjects

CEAP 6 subjects that have met all of the inclusion and none of the exclusion criteria and sign the ICF will be considered 'enrolled' from the moment the first component of the VenaSeal™ delivery system enters the body. Study sites that are not identified at site selection as VLU sites will not be allowed to enroll CEAP 6 patients.

Treatment Outcome Groups:

The subjects will be included in one of the below treatment groups; the required follow-up schedule for all outcome groups is indicated in **Table 5**. In the event that the assigned treatment for the subject is not successfully completed on the first attempt, the reattempt of the procedure can be done on the same day or within 14 days of attempted index procedure per treating physician's discretion. After 14 days, the site should contact the study team to determine next steps.

Table 5: Treatment Outcome Groups

Treatment Outcome	Required Follow-Up
Successful Treatment*: Completion of the assigned treatment including any reattempt to complete the index procedure.	Follow subject schedule per schedule of events and data collection in section 10.1.
Incomplete Treatment*: The index procedure was commenced where the device entered the vasculature, or the surgical stripping procedure was initiated but for any reason full target vein length was not treated.	Follow subject schedule per schedule of events and data collection in section 10.1.
*Subjects with more than one target vein can have a resulting outcome of successful treatment in one vein and incomplete treatment in another. These differing outcomes should be reported on separate Procedure Target Vein CRFs.	
Aborted Procedure: Failed completion of the assigned treatment where the subject was prepped for the index procedure, but the device did not enter the vasculature or surgical stripping was not initiated for any target vein.	Follow subject for 30 days from the date of the attempted index procedure for AE assessment only, which can be completed as a phone call visit if deemed appropriate by the treating physician. Any data collected prior to and during the attempted index procedure, including AE and device deficiency, should be reported on applicable CRFs.
No Procedure (CEAP 2-5): Subject is randomized (considered enrolled) but withdraws from the study after randomization without any attempt to conduct the procedure (e.g., COVID-19 exclusion, subject withdrawal, etc.).	Subject will not be followed in the study for any duration and can exit the study. Complete Study Exit CRF.
Randomization Procedure Not Followed (CEAP 2-5; major protocol deviation): Subject treated with a modality they were not randomized to.	Follow subject schedule per schedule of events and data collection in section 10.1. Report protocol deviation as "randomization procedure not followed".

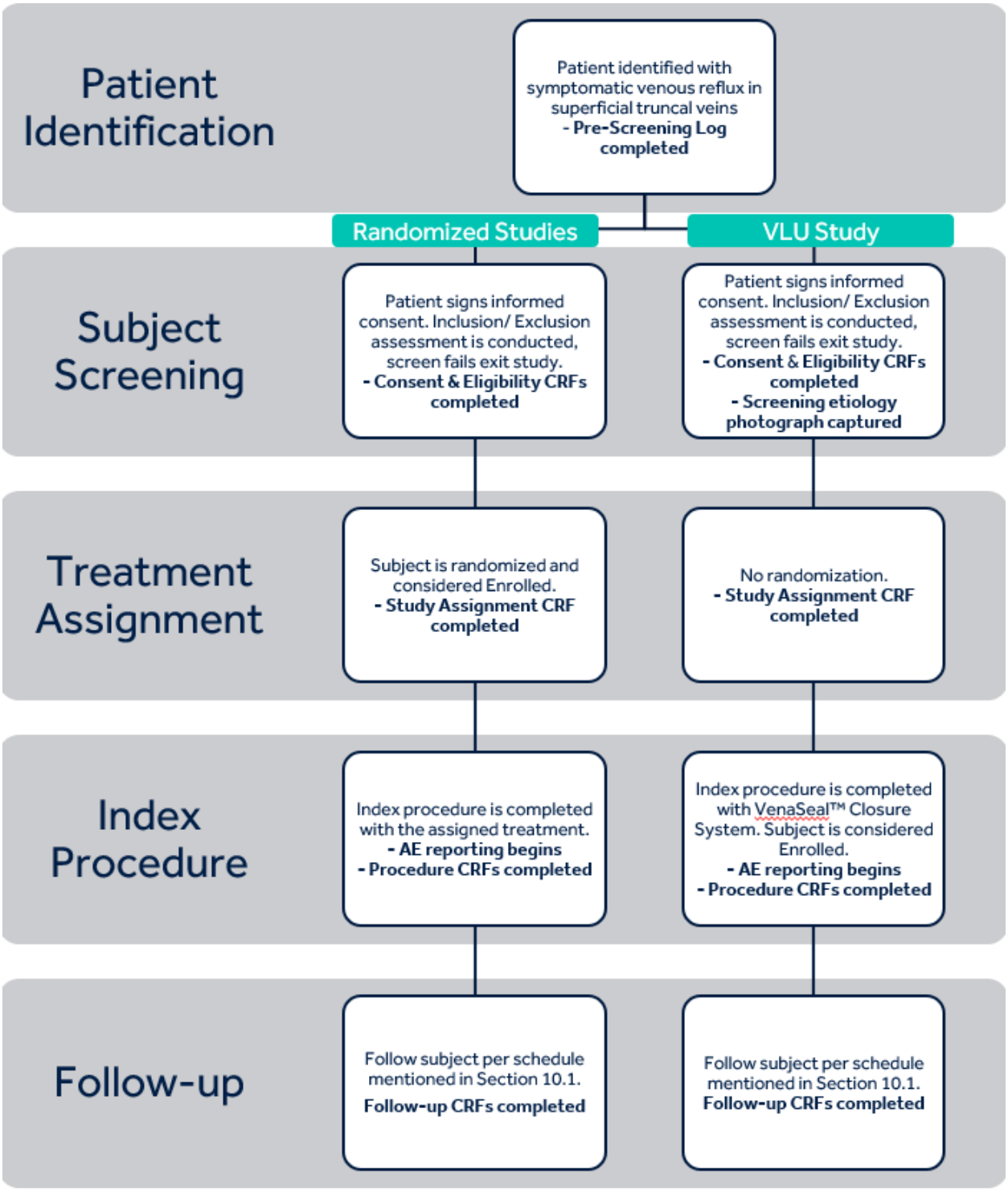

Figure 3: Flow-Diagram from Subject Screening to Follow-up

9.3. Target Veins and Target Limb

Multiple refluxing superficial truncal veins (e.g., GSV, SSV, accessory saphenous veins) in the same target limb that are each at least 10 cm in length may be enrolled and treated in the study. During screening and prior to randomization, sites will identify at least one incompetent target vein. The primary target vein should be the saphenous vein which at the investigator's discretion is most likely responsible for the greatest portion of the patient's symptoms or pathology. The investigator will identify the primary target vein and any additional qualifying target veins to be treated prior to the randomization for CEAP 2-5 subjects and prior to the index procedure for CEAP 6 subjects. The primary target vein will be treated first during the index procedure, and the remaining target veins will be treated in succession.

If more than one vein requires treatment in the target limb, the treating physician will indicate which vein is the primary target vein in the CRFs and track the veins accordingly throughout the study. In the case of bilateral disease with both limbs meeting study eligibility criteria, the investigator should designate the more severe limb (higher CEAP score or most symptomatic according to patient, per treating physician's discretion) target limb. Treatment of the contralateral limb must be staged at least 30 days prior to or at least 3 months post-index procedure.

9.4. Target Ulceration on the Target Limb

At designated VLU sites, patients may be enrolled as CEAP 6 only if ulceration of venous etiology has been identified. Venous etiology will be verified at Screening by the independent core laboratory. The ulceration must be on the target limb. In case of multiple potential wounds within the ulceration, the physician should designate each wound in succession using the image capture equipment provided to sites. Instructions and training will be provided to sites for this purpose.

Circumferential ulcers are not eligible to be included in the study, and the ulcer type will be assessed during the screening visit. It is acceptable for included ulcers to have some curvature, however any curvature around the leg that goes out of sight would be classified as a circumferential ulcer.

Photographs of the target ulceration will be taken at each visit and sent to the core laboratory for assessment. Any ulcer that cannot be captured by one photograph (any ulcer curvature around the leg that goes out of sight) will be considered as a circumferential ulcer and these subjects will not be included in the study. Screening etiology photographs captured as part of routine care within 60 days can also be utilized and sent to the core lab, as deemed appropriate by the treating physician. All wounds on the target limb, as well as any new wounds that develop during the course of the study, should be treated per the investigator's standard of care using approved devices or procedures including wound care, compression therapy, additional superficial vein treatment, and treatment of additional varicosities and incompetent perforating vein(s) required to heal the ulcer.

9.5. Inclusion Criteria

1. Patient is ⩾18 years of age.
2. Patient has venous reflux in superficial truncal vein(s) (e.g., GSV, SSV, accessory saphenous veins) with CEAP category 2 (symptomatic) or CEAP category 3, 4a, 4b, 5, 6 based on the American Venous Forum CEAP classification (2004), appropriate for treatment, as confirmed by DUS.
3. Eligibility for treatment:
   - VenaSeal vs ETA Study: Patient is eligible for treatment with the VenaSeal™ system and ETA.
   - VenaSeal vs Surgical Stripping Study: Patient is eligible for treatment with the VenaSeal™ system and surgical stripping.
   - VLU Study: patients should be eligible for treatment with the VenaSeal™ system.
4. Treatable refluxing segment of target vein(s) 10 cm in length or longer.
5. Patient has a target vein diameter of ⩾3 mm throughout the intended treatment segment of the target vein as measured by DUS while patient is standing.
6. Patient is willing and capable of complying with specified follow-up evaluations at the specified times.
7. Patient has an ability to understand the requirements of the study and to provide informed consent.

9.6. Exclusion Criteria

1. Patient has a known history of allergic sensitivities (including but not limited to cyanoacrylate adhesives), or any other condition, which in the opinion of the investigator may make the patient more susceptible to cyanoacrylate adhesive hypersensitivity.
2. Patient has known deep vein obstruction in the target limb, as identified by the site's standard of care.
3. Patient has abnormal pulse exam or ABI <0.8.
4. Patient has acute superficial thrombophlebitis.
5. Patient requires any non-target vein treatments in the contralateral or ipsilateral limb, or any other surgical procedure up to 30 days pre-procedure and through 3 months post-procedure.
6. Patient has any 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).
7. IFU contraindications:
   - VenaSeal vs. ETA Study: Patient has VenaSeal™ system and/or ETA product's IFU contraindication(s).
   - VenaSeal vs. Surgical Stripping Study: Patient has surgical stripping and/or VenaSeal™ system IFU contraindication(s).
   - VLU Study: Patient has VenaSeal™ system IFU contraindication(s).

8. Patient is non-ambulatory.
9. Patient is a female of childbearing potential who may be pregnant or breastfeeding at the time of the index procedure. *
10. 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.
11. Patient is currently participating in an investigational drug or device study when the data collected could be conflicting or biased due to participation in another study.
12. Patient has documented COVID-19 infection currently or within the past 3 months. Patient is not completely recovered from past COVID-19 infection, per physician's discretion.
13. VLU Study: Patient has target ulceration identified to be of non-venous etiology, as confirmed by the independent core laboratory.
14. VLU Study: Patient has target circumferential ulceration that cannot be captured in a single photograph (any ulcer curvature around the leg that goes out of sight).

Note: CEAP 6 VLU patients are excluded at sites not identified as VLU Study sites.

*Pregnancy to be assessed per treating physician's routine practice; testing is not required if verbal confirmation is preferred. Breastfeeding patients may be included if mother's expressed milk is discarded surrounding the index procedure, per the treating physician's standard instructions. Sites must document routine methods utilized for such patients.

10. Study Procedures

10.1. Schedule of Events and Data Collection

An overview of all data collection requirements is given in **Table 6** and **Table 7** below. All subjects (in the Randomized Studies as well as the VLU Study) will follow the assessment schedule in Table 6, and VLU Study subjects will also follow the assessment schedule in Table 7, until healing per the CIP definition has occurred. Study-specific assessments may not occur until the ICF has been obtained, and only trained/delegated personnel may conduct study specific assessments. Subjects should return to the study site for their study visits; other local hospitals or clinics should not be used as an alternative.

Some study follow-up visits are not routine care. Routine care post-procedure differs from site to site. However, follow-up visits that are not routine care are not considered burdensome and/or invasive.

Table 6: Schedule of Assessments – All Subjects

Data Collection Requirement	**Screening**	**Baseline** (<30 days before procedure)	**Index Procedure** (Day 0)	**Day 7** (± 2 days)	**Day 30** (± 7 days)	**3+ Months Adjunctive Therapy** (Optional)	**6 Months** (± 4 weeks)	**12 Months** [1] (± 8 weeks)	**24, 36, 48 and 60 Months** (± 8 weeks)	**Unscheduled**[2]
Informed Consent	X									
CEAP Clinical Classification (2004 and 2020)	X						X	X	X	X
Randomization	X									
Demographics, Medical History		X								
Concomitant Medications		X	X							
rVCSS		X		X	X		X	X	X	X
Patient-Reported Symptoms		X		X	X		X	X		
EQ-5D-5L QoL		X			X		X	X	X	
AVVQ QoL		X			X		X	X	X	
SF-36 QoL		X			X		X	X		
VenousTSQ[3]					X		X	X		
Duplex Ultrasound		X[4]	X	X	X		X	X	X	X
Procedure-related Data & Outcome			X							
Physician Satisfaction with Procedure			X							
Patient-Reported Outcomes				X	X		X	X	X	
Reintervention Review				X	X		X	X	X	
Healthcare utilization				X	X		X	X	X	
Adjunctive Therapy Assessment						X	X	X	X	
Adverse Event Assessment			X	X	X	X	X	X	X	X
Device Deficiency Assessment			X							

[1] Subjects in VenaSeal vs. Surgical Stripping Study will be followed through 12 months only.

[2]AE assessments at unscheduled visits are required. Additional assessments are per investigator's discretion; see section 10.11 for additional detail

[3] VenousTSQe captured at 30 Days; VenousTSQs captured at 30 Days, 6 Months and 12 Months

[4] Sites to utilize their standard of care DUS to assess screening criteria, within 6 months of the Screening/Baseline visit; if not conducted in a standing position, sites will need to re-image patient for target vein measurements only

Table 7: Additional Schedule of Assessments – VLU Study

Data Collection Requirement	Screening	Baseline	Procedure	7 & 30 Days	2, 3, 4, & 5 Months (+/- 7 days)	6 Months	8 & 10 Months (+/- 2 weeks)	12 Months	24, 36, 48, & 60 Months	Healing Verification (<2 weeks of healing)
All-Subject Requirements and Visit Windows from Table 6	*X*	*X*	*X*	*X*		*X*		*X*	*X*	
Etiology Photograph	X									
Target Active Ulcer Assessment		X		X	X	X	X	X		
Ulcer-specific Healthcare Utilization				X	X	X	X	X	X	X
Active Ulcer or Healing Verification Photograph		X[1]		Photographs captured at each visit until healing is demonstrated through 24 months.						X[2]
Adverse Event Assessment			X	X	X	X	X	X	X	X
Ulcer Healing and/or Recurrence Assessment				X	X	X	X	X	X	X
Active Ulcer Wound Care	Wound care and compression therapy to proceed per routine care until healing is demonstrated.									

[1] Index procedure should occur within 7 days of baseline ulcer photograph. If the baseline visit is more than 7 days out from the index procedure, photographs should instead be taken on the day of the index procedure, prior to the start of the procedure.

[2] Healing verification to be captured through 24 months, as applicable.

10.2. Scheduled Follow-up Visit Windows

The target visit dates for the subject that gets enrolled in the study can be obtained via 'Visit Scheme' CRF from the study database. Should a subject miss a visit or if the visit falls outside of the pre-specified window, a study deviation must be reported, and the original follow-up schedule should be maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Follow-up visit windows are listed in **Table 8** and **Table 9** and are based on days post-procedure.

Table 8: Follow-up Visit Window – All Subjects, VenaSeal vs Surgical Stripping Study will follow this schedule to 12 months

Study Follow-up Visit	**Window (Calculated days post index procedure)**		
	Window Start (days post-procedure)	Target (days post-procedure)	Window End (days post-procedure)
Day 7	5	7	9
Day 30	23	30	37
6 Months	154	182	210
12 Months	309	365	421
24 Months	674	730	786
36 Months	1039	1095	1151
48 Months	1404	1460	1516
60 Months	1769	1825	1881

Table 9: Additional Follow-up Visit Window – VLU Study

Study Follow-up Visit	Window (Calculated days post index procedure)		
	Window Start (days post-procedure)	Target (days post-procedure)	Window End (days post-procedure)
2 Months	53	60	67
3 Months	83	90	97
4 Months	113	120	127
5 Months	143	150	157
8 Months	226	240	254
10 Month	286	300	314

10.3. Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an ICF that has been approved by the study site's IRB/EC/CA and signed and dated by the subject. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the informed consent along with the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be approved by the IRB/ EC/CA. The document must be controlled (i.e., versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB/EC/CA. Any adaptation of the template ICF must be reviewed and approved by Medtronic and the IRB/EC/CA reviewing the application prior to enrolling subjects.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

The study informed consent is available under a separate cover. Prior to initiation of any study-specific procedures, informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit

subject information to the study sponsor. The informed consent process must be conducted by the PI or an authorized designee, and the ICF along with Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject in a language he/she is able to read and understand. The process of informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The informed consent process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the ICF must be signed and personally dated by the subject and investigator or authorized designee, as required by the ICF, and ensured by the PI or his/her authorized designee.

A copy of the ICF along with the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, signed and dated as required by law, must be provided to the subject.

If the informed consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, the informed consent process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. The ICF and any other information must be read aloud to the prospective subject or his/her legally designated representative. Whenever possible, either the subject or his/her legally designated representative shall sign and personally date the ICF. The witness signs and personally dates the ICF attesting that the information was accurately explained and that informed consent was freely given.

The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

The ICF along with Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing.

Consistent with the Declaration of Helsinki, vulnerable adults (i.e., those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g., Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. If the ICF is signed by an individual other than the subject, the monitor may discuss whether the Investigator believes the subject meets the definition of a vulnerable adult. This protocol defines vulnerable adult as those subjects mentally incapable of giving consent, in the Investigator's opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response." For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

10.4. Randomization and Treatment Assignment (CEAP 2-5)

After a patient has signed the ICF, the CEAP assessment has been completed, and the eligibility criteria are verified, the patient will be enrolled via randomization. There are two Randomized Studies:

1. VenaSeal vs. ETA Study: subjects will be 1:1 randomized to VenaSeal™ system or ETA treatment.
2. VenaSeal vs. Surgical Stripping Study: subjects were randomized 1:1 to VenaSeal™ system or surgical stripping treatment. VenaSeal vs Surgical Stripping Study was closed to enrollment as of 22-Feb-2022.

Each site will be designated as participating in only one of the two Randomized Studies and cannot participate in both. Which study the site will enroll into is pre-determined by geographical region and device/treatment availability (i.e., regulatory approval and reimbursable status). Randomization will be accomplished using the Oracle Clinical system (or paper back-up if the system is down) prior to the collection of Baseline visit data and will be stratified by the site and by CEAP (2004) clinical category to ensure balanced arms. Site personnel will obtain the subject's randomization sequence on the Randomization CRF which will be generated from the database. Randomization schedules will be prepared for each site using a random permuted block design stratified by site and CEAP (2004) (grouping categories 2-3 vs. 4-5).

If a subject is inadvertently randomized twice or more, the first assigned treatment arm will be used for the intention-to-treat analysis, and investigators should treat subjects according to the first randomization. Knowledge of the development of randomization lists may lead to selection bias, therefore these details will be described in a separate document. If a subject is inadvertently treated with the wrong treatment modality, this will be recorded as a protocol deviation.

Randomization may be done during the screening visit as applicable or may be completed closer to the Baseline visit if there will be a significant delay between Screening and Baseline.

CEAP 6, active VLU subjects will not be randomized and will be treated with the VenaSeal™ system.

10.5. Study Assessments

CEAP Classification

At screening and at 6, 12, 24, 36, 48 and 60 months, the American Venous Forum CEAP classification (2004) will be used to provide a comprehensive objective classification of the severity of the target limb **(CEAP Classification)**. CEAP describes the clinical manifestations (C), etiologic factors (E), anatomic distribution of disease (A), and underlying pathophysiologic findings (P). This study will only collect the clinical manifestations classification. This assessment must be performed for the target limb. The CEAP Classification needs to be assessed by a physician or qualified delegated person. Alternatively, it can be assessed by a nurse practitioner per their license or training. Recently, an updated CEAP classification (2020) was published by Lurie et al.[17] The 2020 clinical manifestation of the CEAP classification will be collected for analysis purposes but will not be used to determine the patient's eligibility as part of this study.

Revised Venous Clinical Severity Score (rVCSS)

The revised VCSS will be used to assess baseline venous disease status as well as changes in venous disease severity over time (**rVCSS**). As such, the rVCSS should be assessed for the target limb at baseline and at 7 days, 30 days, 6, 12, 24, 36, 48 and 60 months. At Unscheduled visits, the rVCSS should be taken before an intervention in the target vein takes place; if an intervention is not occurring, it can be completed at the treating physician's discretion. The rVCSS needs to be assessed by a physician or qualified delegated investigator. Alternatively, the rVCSS can be assessed by a nurse practitioner per their license or training.

Duplex Ultrasound

It is expected that patients approached for study enrollment will have undergone a standard of care DUS to diagnose the patient's VRD; this routine imaging can be utilized up to 6 months prior to the Screening visit. DUS images will be performed by DUS technicians or investigators trained and delegated to the study. Target vein measurements will be collected from this DUS if conducted while the patient was

standing; if not, the DUS must be repeated solely to measure the target vein(s) diameter at the proximal, mid, and distal points, as well as the widest part of the vein. Additional instructions for target vein measurements will be provided under a separate cover.

Post-index procedure, DUS evaluation is required to assess target vein (including primary target vein) closure after VenaSeal™ system or ETA treatment and absence of refluxing vein or residual vein after surgical stripping. DUS is also used for thrombus assessment. This DUS assessment will also be performed at 7 days, 30 days, 6, 12, 24, 36, 48 and 60 months. This DUS assessment could be completed on the day of the follow-up visit or anytime during the follow-up visit window, as applicable to the site's standard scheduling process.

Patient-Reported Symptoms

Subjects will be asked to report symptoms related to their target limb: pain, aching, itching, burning, sensitivity, heaviness and swelling, and asked to identify their dominant symptom from this list. This will be assessed at baseline and at follow-up visits through 12 months. These questions must be completed by the subject and a translation will be available in each of the applicable languages; however, designated site staff may verbally read the symptom list to the patient.

Venous Treatment Satisfaction Questionnaire (VenousTSQ)

The two components of the VenousTSQ are evaluated as two separate primary endpoints in this study. The questionnaire needs 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. This should be the first subject-reported assessment at all study visits when administered.

The Venous Treatment Satisfaction Questionnaire (VenousTSQ) is a new Patient Reported Outcome Measure (PROM). Via a qualitative design approach involving patient interviews and clinical expert reviews, the process resulted in an independently developed tool for venous patients. The tool consists of two components, the peri-procedural early component of treatment satisfaction which will be measured at 30 days post index-procedure (VenousTSQe), and the longer-term status component of treatment satisfaction which can be measured at 30 days, 6 and 12 months (VenousTSQs). Questions focus on topics relevant for patients with varicose veins who have undergone a venous treatment and include items on treatment satisfaction/dissatisfaction, symptoms such as pain, and outcome satisfaction/dissatisfaction.

At the time of the finalization of this investigation plan, partial validation of the VenousTSQ has taken place while the remaining validation steps are being carried out during a psychometric analysis. Part of the development and validation process of the VenousTSQ is a quantitative psychometric analysis that is carried out independently to determine the internal consistency and reliability of the tool and that will

ultimately lead to the scoring guidelines. The quantitative psychometric analysis will be carried out within the study on the 30-day data of at least 100 subjects from predominately English-speaking countries (e.g., US, UK, Australia, and Canada) who are enrolled as part of this study. In addition, confirmatory linguistic validation on other languages may be performed. Where applicable, subjects will be asked for their consent for this separately because part of their non-identifying data may be shared with the independent developer of this questionnaire.

Quality of Life

Health-related Quality of Life (QoL) outcomes will be assessed at baseline, day 30 and months 6, 12, 24, 36, 48, and 60 using the AVVQ, EQ-5D-5L and SF-36 questionnaires **(Appendix A: Patient Questionnaire and Assessments).** 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.

- AVVQ: a venous-disease specific QoL measure including 13 questions that each correspond to one of four clinically recognizable aspects of health, being 1) pain and dysfunction, 2) cosmetic appearance, 3) extent of varicosity, 4) complications.
- EQ-5D-5L: a two-component tool consisting of a descriptive part that evaluates five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the EQ-VAS, a vertical, visual analog scale, used for self-reporting on health.
- SF-36: a 36-item generic QoL tool measuring health across three dimensions and including eight separate scales: 1) functional status (including physical functioning, social functioning, role limitations attributed to physical problems, and role limitations attributed to emotional problems), 2) wellbeing (including mental health, energy and fatigue, and pain), and 3) overall evaluation of health (including general health perception).

Other Patient-Reported Outcomes

- Pain score will be collected during the index procedure and at 7 days and 30 days.
- Return to work and return to normal activities will be assessed at follow-up visits until the subject has returned to each.
- The VenousDQoL consists of two stand-alone questions at baseline, 7 and 30 days, 6, 12, 24, 36, 48 and 60 months (data will be collected through 12 months for subjects enrolled in VenaSeal vs. Surgical Stripping Study).

Questionnaire completion by delegated site personnel

The required study questionnaires such as EQ-5D-5L, VenousTSQ, patient reported symptoms, etc. should be completed in a consistent manner throughout the study. Selecting to complete the required questionnaire on behalf of the subjects should only be if the subjects require it (e.g., vision or literacy issues) and not simply by site or patient preference. The site personnel completing the questionnaire

cannot be the treating physician or the PI in order to avoid any bias. If site personnel are assigned to complete the questionnaire on behalf of the subject for one visit, then site personnel should complete for all the remaining visits. Site personnel have to read the complete questionnaire including all the response options. Ideally, the same person will complete the questionnaire with the same subject each time, if at all possible. The questionnaires completed by site personnel may differ from subject questionnaires and may require IRB/EC approval. If necessary, due to COVID-19 restrictions, these questionnaires could also be completed and signed by the subject within 24 hours prior to the follow-up visit. If captured in this manner, care must be taken to ensure the questionnaires are completed and returned to the site prior to the completion of the rest of the visit.

Healthcare Utilization

This study will collect healthcare utilization data related to subject's VRD and care related to the VenaSeal™ closure system to demonstrate total costs over the follow-up period. Specifically, this study will collect:

- Number and type of adjunctive treatments (phlebectomy and sclerotherapy) conducted through 60 months post-index procedure.
- Subject's healthcare utilization related to their target limb VRD, as determined by medical record review and/or subject's report of healthcare visits conducted and other health-related resources utilized (e.g. home healthcare services) between study visits.
- Procedures, tests and treatment of AEs related to the VenaSeal™ system or the index procedure, as reported by sites in AE reporting.
- VLU Study: Subject's healthcare utilization and routine wound care treatments between follow-up visits through 60 months.

VLU Assessment on the target limb

Patients who enter the study at designated VLU sites with an active VLU (CEAP 6) on the target limb will receive wound care and compression therapy per the site's standard of care for their VLUs, and undergo ulcer assessments at screening, baseline and each follow-up visit until the ulcer is healed.

At the Screening visit, after consent has been obtained, target limb ulceration will be photographed by the provided eKare imaging equipment to assess etiology and if circumferential. Any ulcer curvature around the leg that extends out of sight and that cannot be captured in a single photograph would be considered as a circumferential ulcer and such subjects will not be included in the study. These photographs captured as part of routine care within 60 days can also be utilized, as deemed appropriate by the treating physician. Photographs will be submitted to the core laboratory to assess venous etiology within 3 business days. If the core laboratory concludes that the ulcer is of non-venous etiology, then the subject will be considered as a screen failure and exited from the study. The baseline ulceration

photographs must be taken within 7 days of the index procedure. If the baseline visit is scheduled more than 7 days from the index procedure, the site may collect all remaining baseline data and hold off on taking the photographs until the day of the index procedure, prior to the start of the procedure. The baseline photographs will be sent to the core laboratory for assessments.

Follow-up target limb ulcer assessments will take place at Day 7, Day 30, Months 2, 3, 4, 5, 6, 8, 10, and 12 or until healing has occurred. If the healing has not occurred at 12 months, subjects will revert to the annual visit schedule and continue to follow standard wound care unless healing occurs, and a healing verification visit is necessary. If healing occurs past 24 months, subjects will no longer undergo a healing verification visit. When all target limb ulceration has healed, subjects will have an ulcer healing verification visit (up to 24 months) as outlined in section 10.12.

Photographs will be taken of active ulcers and at the healing verification visit using the eKare insight® 3D wound imaging system provided to VLU sites. Multiple photographs will be captured: 1) one 3-dimensional photo for the measurements and 2) a standard, 2-dimensional photo of a wider view of the index limb. The ulcer size will be assessed, and complete healing will be confirmed by the wound core laboratory via these photographs provided by the study site. Core laboratory assessment is also described in section 13.3.

If the ulcer on the target limb recurs, this will be reported in the CRF during study follow-up visits. The ulcer status compared to the last study visit (e.g., healed, recurred, or healed and recurred) will be collected at each visit. In addition, type of the wound care received since last visit including debridement, skin graft, dressing change, Unna boots or any other treatment will be recorded in the CRFs at each follow-up visit until initial ulcer healing is confirmed. An ulcer core laboratory manual and site training will be provided to sites for further details on the photograph process.

New ulcers not related to the original ulceration that develop post-index procedure but prior to initial healing may need to be reported as AEs (if considered worsening of disease) and will undergo ulcer assessments as described here for all ulcers. New ulceration that develops following healing confirmation will be considered ulcer recurrence and will not be assessed as described here, however may need to be reported as AEs.

10.6. Screening

During the screening visit, the site will conduct the following:

1. Informed consent.
2. Subject evaluation for inclusion/exclusion criteria: Sites should utilize their routine care diagnostic DUS from within 6 months of the screening visit, or repeat this DUS if greater than 6 months old.

3. CEAP clinical classification.
4. VLU Study: Photographs to assess ulcer venous etiology and exclude circumferential ulcers. These photographs captured as part of routine care within 60 days can also be utilized as deemed appropriate by treating physician. Photos must be submitted to the core laboratory and confirmed as venous etiology prior to moving on to the Baseline visit.

Sites may randomize the patients in the Randomized Studies following the Screening Visit data collection and confirmation of inclusion/exclusion criteria.

10.7. Prior and Concomitant Medications

The current use of the following medications will be collected at the Baseline visit:

1. Anticoagulants (e.g., Warfarin, NOAC, Lovenox)
2. Antiplatelets/Aspirin/$P2Y_{12}$-inhibitors
3. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
4. Other pain medication.

Medications given as part of the index procedure will also be documented. Medications used for treatment of any AEs will be tracked during the AE assessment. Additional concomitant medications will not be recorded for study purposes.

10.8. Baseline (within 30 days prior to index procedure)

The Baseline visit may be combined with the index procedure visit if the site chooses, so long as the Baseline data is collected prior to the index procedure.

VLU Study: wound care and compression therapy should be initiated per the site's standard of care and as early as possible (e.g., after confirmation of venous etiology by the core laboratory), if it is not ongoing already.

During the Baseline visit, the site will collect the following:

1. Demographics, as able to be collected per the site's regional regulations.
2. Targeted medical history and concomitant medications, limited to items potentially related to the subject's VRD as indicated in the CRF specifications provided separately.
3. Baseline DUS: If routine care DUS was not conducted in a standing position, sites will need to re-image patient for target vein measurements only.
4. rVCSS
5. AVVQ QoL questionnaire

6. EQ-5D-5L QoL questionnaire
7. SF-36 QoL questionnaire
8. Venous DQoL
9. Patient-reported symptoms and indication of their dominant symptom.
10. VLU Study: Ulcer assessment on target limb including ulcer photograph for submission to core laboratory. The baseline ulcer photograph must be taken within 7 days prior to the index procedure. If the Baseline visit is more than 7 days prior to the index procedure, then photographs should be collected at the index procedure before the start of the procedure.

10.9. Index Procedure

For the Randomized Studies, subjects must undergo the procedure for which they were randomized to. Subjects treated with a modality they were not randomized to will be considered a major protocol deviation. CEAP 6 subjects in the VLU Study will not be randomized and will all be treated with the VenaSeal™ system.

The index procedure should be performed according to the current and applicable version of the manufacturer's IFU (if applicable) to the region of the study site. AE reporting for all subjects (Randomized Studies and VLU Study) will begin from the moment the index procedure is initiated, in line with the reporting requirements described in section 12: Adverse Events and Device Deficiencies of the protocol.

All Subjects:

The primary target vein must be treated first during the index procedure, and the remaining target veins will be treated in succession.

Procedure for VenaSeal™ closure system (CEAP 2-5 subjects in Randomized Studies assigned to VenaSeal™, or CEAP 6 subjects in VLU Study):

Prophylactic medications for potential allergic reaction to VenaSeal™ adhesive may be administered to the subject per the treating physician's discretion. Compression therapy and wound care dressings (VLU subjects) will be removed prior to the start of the procedure, if applicable.

Local anesthetic including tumescent and light sedation (including but not limited to oral Xanax and Valium) may be utilized. All other types of anesthesia including general, regional, and heavy sedation are not permitted for the VenaSeal™-treated subjects.

The IFU for the VenaSeal™ system applicable per region should be referred to for the procedure.

Procedure for surgical stripping (CEAP 2-5 subjects in Randomized Studies assigned to surgical stripping):

All types of anesthesia including general, heavy and light sedation, regional or local anesthesia may be used, per site's standard practice. Compression therapy will be removed prior to the start of the procedure, if applicable.

Surgical stripping was performed per physician's or site's standard practice. Enrollment was closed as of 22-Feb-2022 in the VenaSeal vs. Surgical Stripping Study.

Procedure for ETA (CEAP 2-5 subjects in Randomized Studies assigned to ETA):

Local anesthetics including tumescent and light sedation (including but not limited to oral Xanax and Valium) may be utilized. All other types of anesthesia including general, regional, and heavy sedation are not permitted for the ETA-treated subjects. Compression therapy use will be removed prior to the start of the procedure, if applicable.

The subject can be treated with either RFA or EVLA per site's standard practice and treating physician's discretion. Also, any RFA or EVLA device approved in the site's region can be used per site's standard practice. The manufacturer's current IFU applicable per region should be referred to for the procedure.

Adjunctive Therapies & Treatments

If the target limb is CEAP 4b, or 5, incompetent perforating veins may be treated per the investigator's standard of care using approved devices or procedures during the index procedure. If any other devices are used during the index procedure to treat the incompetent perforating veins, then data will be collected on other devices as applicable. The devices used for the incompetent perforating veins procedure should have regulatory approval applicable per region. If the incompetent perforating veins are treated post index procedure (permitted 3 months after index procedure) for CEAP 4b or 5 target limb, then data will be collected from 3 months through study end.

VLU Study: For CEAP 6 subjects, incompetent perforating veins may be treated per the investigator's standard of care using approved devices or procedures during the index procedure or at any time after the index procedure. If any other devices are used during or after the index procedure to treat the incompetent perforating veins, then data will be collected on other devices as applicable throughout the study. The devices used for the incompetent perforating veins procedure should have regulatory approval applicable per region.

VLU Study: Foam sclerotherapy may be injected into the ulcer bed, per site's standard of care. Subjects with VLUs will continue with ongoing wound care therapy, or have it initiated, as directed by a wound care physician until wound healing has been verified by the core laboratory.

For subjects undergoing surgical stripping, adjunctive procedures such as phlebectomy of tributaries can be performed during the index procedure, per the treating physician's discretion. For ETA or VenaSeal™ subjects, any adjunctive treatment of varicosities in the target limb such as phlebectomy or sclerotherapy cannot be performed along with the index procedure.

Subjects for all studies may return to the site after 3 months (calculated as 90 days) following the index procedure to complete additional adjunctive therapies of target limb varicosities per the treating physician's discretion; these treatments will be considered routine care. The data for the adjunctive therapy treatment will be collected through 60 months.

Other truncal veins in the non-target limb may not be treated at the time of the index procedure or within 30 days prior to or 3 months post-index procedure.

Post-Procedure

At the completion of the procedure, when treatment of all target veins has been completed, vessel occlusion (VenaSeal™ or ETA) or absence of refluxing target vein or residual target vein (surgical stripping) will be confirmed by DUS. Subjects should be provided pain, allergy and/or anti-coagulant medication at the treating physician's discretion as appropriate for the treatment received. Upon discharge, subjects should follow the site's standard post-operative instructions.

At the index procedure visit, the following procedural data shall be recorded for each subject in the study:

1. Date of procedure.
2. Code for physician conducting the procedure, as indicated in a coded log provided to sites.
3. VenaSeal-randomized and CEAP 6 subjects: Number of VenaSeal™ system procedures the treating physician has completed to date.
4. VenaSeal-randomized and CEAP 6 subjects: Identification data of the VenaSeal™ kits utilized for treatment.
5. Procedure times as described in the CRF specifications.
6. Medications: anesthetic, prophylactic, and post-procedural medications.
7. Pre-procedure length measurement of clinically relevant superficial truncal disease in target veins with a tape measure applied outside of the target limb prior to sterile field.
8. Chosen vein access sites for each target vein as well as type of access utilized.
9. Distance of vein access from the tibial tuberosity, if below the knee.

10. VenaSeal-treated subjects: points of aneurysm, tributaries, or perforators per target vein when multiple VenaSeal™ aliquots are utilized.
11. Post-procedure DUS: assessment of patency, stump length, reflux along treatment area, evidence of thrombus.
12. Post-procedure measurement of actual treatment length using a tape measure to measure the difference between the clinically relevant lowest point of reflux to the access point.
13. Physician satisfaction with the procedure.
14. AE assessment from the moment the index procedure was initiated.
15. VenaSeal™ system treated subjects: Device deficiencies related to the VenaSeal™ system.
16. Treatment issues experienced by the treating physician.
17. Subject's use of compression stockings upon discharge.

10.10. Follow-Up Visits: All Subjects

The VenaSeal vs Surgical Stripping Study patients will stop any follow-up assessments after the 12-month visit.

Day 7 (+/- 2 days)

Patients will return to the site for follow-up for the following assessments (limb-specific assessments are of the target limb only):

1. DUS:
   a. Areas of patency, if any
   b. Reflux along treatment area
   c. Evidence of thrombus
2. rVCSS
3. Patient reported outcomes:
   a. Pain score measured by using NRS scale of 0-10
   b. Patient-reported symptoms
   c. Ability to return to work/normal activities
   d. VenousDQoL
4. AE assessment
5. Healthcare utilization since last study visit
6. VLU Study:
   a. Active ulcers: ulcer assessment, ongoing wound care, photographs for core laboratory, healing status
   b. Post-healing confirmation: recurrence status.

Day 30 (+/-7 days)

1. DUS:
    a. Areas of patency, if any
    b. Reflux along treatment area.
    c. Evidence of thrombus
2. rVCSS
3. Peri-procedural Venous Treatment Satisfaction Questionnaire (VenousTSQe) and Venous Treatment Satisfaction Questionnaire (VenousTSQs)
4. EQ-5D-5L
5. AVVQ
6. SF-36
7. Patient reported outcomes:
    a. Pain score measured by using NRS scale of 0-10
    b. Ability to return to work/normal activities (only if not returned to work/normal activities by 7-day visit)
    c. VenousDQoL
    d. Patient-reported symptoms
8. AE assessment
9. Healthcare utilization since last study visit
10. VLU Study:
    a. Active ulcers: ulcer assessment, ongoing wound care, photographs for core laboratory, healing status
    b. Post-healing confirmation: recurrence status.

If COVID-19 prevents patients from returning for follow-up visits at 7 or 30 days (due to subject contracting COVID-19 or due to site policy), these visits may be conducted through telehealth or other alternative methods to be discussed with the Medtronic study team prior to execution.

3+ Months (calculated as 90 days): Optional for all subjects

1. Adjunctive therapy: Number of phlebectomy sites and/or sclerotherapy injections administered (data collected through 60 months).
2. AE Assessment.

6 months (+/- 4 weeks), 12, 24, 36(+/-8 weeks)

Subjects will return to the site for follow-up to conduct the following assessments (limb-specific assessments are of the target limb only). VenaSeal vs Surgical Stripping Study subjects will be followed up to and including 12 months:

1. DUS:
    a. Areas of patency, if any
    b. Reflux along treatment area
    c. Evidence of thrombus
2. CEAP classification
3. rVCSS
4. Venous Treatment Satisfaction Questionnaire (VenousTSQs) (up to 12 months visit)
5. EQ-5D-5L
6. AVVQ
7. SF-36 (up to 12-month visit)
8. Patient reported outcomes:
    a. VenousDQoL
    b. Patient-reported symptoms (up to 12-month visit)
9. Adjunctive therapy assessment
10. AE assessment
11. Healthcare utilization since last study visit
12. VLU Study:
    a. Active ulcers: ulcer assessment, ongoing wound care, photographs for core laboratory, healing status
    b. Post-healing confirmation: recurrence status.

48, 60 months (+/-8 weeks)

Subjects will return to the site for follow-up to conduct the following assessments (limb-specific assessments are of the target limb only). Subjects may also complete 48 and 60 months visit remotely per physician's discretion if subjects cannot return to the site for follow-up.

1. DUS:
    a. Areas of patency, if any
    b. Reflux along treatment area
    c. Evidence of thrombus
2. CEAP classification
3. rVCSS
4. EQ-5D-5L
5. AVVQ
6. Patient reported outcomes:
    a. VenousDQoL
7. Adjunctive therapy assessment
8. AE assessment
9. Healthcare utilization since last study visit
10. VLU Study:
    a. Active ulcers: ulcer assessment, ongoing wound care, healing status
    b. Post-healing confirmation: recurrence status.

If remote visit occurs, the following assessments can be completed via telehealth and/or hard-copy of questionnaires required to be completed via mail. Questionnaires can be sent to subjects via mail and subjects can complete and return it back to the site via mail.

1. EQ-5D-5L
2. AVVQ
3. Patient reported outcomes:
    a. VenousDQoL
4. AE assessment
5. Healthcare utilization since last study visit
6. VLU Study:
    a. Active ulcers: ulcer assessment, ongoing wound care, healing status
    b. Post-healing confirmation: recurrence status

10.11. Unscheduled Visits

A visit outside of the study follow-up schedule will be reported as unscheduled study visit if it was conducted for the evaluation of an AE per the AE reporting requirements in this study. In addition to any applicable AE treatment or diagnostic testing, the following additional assessments may be completed, per the treating physician's discretion (limb specific assessments are of the target limb only):

1. Required: AE assessment
2. CEAP classification
3. rVCSS
4. DUS.

10.12. Additional Follow-Up Visits: VLU Study Active Ulcers

2, 3, 4, 5 (+/- 7 days), 8, 10 Months (+/- 2 weeks) until Healing Verification

Ulcer assessments on the target limb will take place at standard study visits (Screening visit, Baseline visit, Day 7, Day 30, and 6, 12, 24, 36, 48 and 60 months). In addition, visits at 2, 3, 4, 5, 8, and 10 Months will be conducted for active ulcers, until healing has occurred and been verified. If complete healing has not occurred by 24 months, subjects will continue to follow standard wound care and remaining study visits. At these active ulcer visits, sites will conduct the following assessments:

1. Active ulcer assessment
2. Ongoing wound care
3. Ulcer-specific healthcare utilization
4. Photographs for core laboratory
5. Healing and/or recurrence assessment
6. AE assessment.

Ulcer Healing Verification Visit

Once the site research team has been informed of all wounds healing on the target ulceration by the wound care center, the subject will undergo an ulcer healing verification visit within 2 weeks of ulcer healing to confirm healing and collect photographs of the ulcer. The ulcer assessment core laboratory will verify healing. If core laboratory does not confirm healing with the first set of photographs, the subject will return in 1 week for additional photographs to be collected and sent to the core laboratory. If the core laboratory does not confirm healing after the second set of photographs, but the treating physician believes the ulcer has healed, the ulcer will be classified as healed. The ulcer healing verification visit may occur up to 24 months, after which core lab ulcer imaging for wound healing will not be required. Data will continue to be collected for healing and recurrence status changes through 60 months.

10.13. Assessment of Effectiveness

Procedure effectiveness will be measured as primary target vein and target vein closure, defined as DUS showing closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm after ETA or VenaSeal™ system treatment and absence of refluxing vein or residual vein after surgical stripping. It will also be measured as elimination of clinically relevant superficial truncal disease in target vein at the time of index procedure in addition to reintervention and time to reintervention of a target vein (including primary target vein) through 60 months (through 12 month visit for subjects randomized to the VenaSeal vs. Surgical Stripping Study) assessed at each follow-up visit (except 7 days) until reintervention occurs or the study ends.

Ulcer healing effectiveness will be measured by time to ulcer healing, percent area healing per month and absolute healing, as verified by the independent core laboratory.

10.14. Assessment of Safety

An AE assessment will take place at each follow-up visit (from the moment the index procedure is initiated until completion of follow-up or study exit). Reports of AEs and device deficiencies (refer to section 12) will be evaluated by Medtronic. The CEC will review and adjudicate events in accordance with section 13.1 Additional details are outlined in the CEC Charter.

10.15. Recording Data

This study will utilize a Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Each enrolled subject will be assigned a unique study ID number, which is pre-configured in the RDC system. Records of the subject/subject ID relationship will be maintained by the study site. Individual subject medical information obtained for this study will be considered confidential. The subject's medical charts must be clearly marked to indicate that subjects are enrolled into the study, per the site's Standard Operating Procedures (SOPs).

Required data will be recorded on electronic case report forms (CRFs) by authorized site personnel as indicated on the Delegated Task List (DTL), which can be found in the Investigator Site File (ISF). Study personnel delegated for CRF completion will be trained on the use of the RDC system and thereafter provided with a username and password to access the system. The CRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study. The investigator (or delegated co-investigator) will electronically sign the appropriate pages of each CRF.

The RDC system maintains an audit trail of entries, changes, and corrections in CRFs. If a person only authorized to complete CRFs makes changes to an already signed CRF, the investigator shall re-approve that CRF.

The investigator must ensure accuracy, completeness, legibility and timeliness of the data reported in the CRFs and in all other required reports. 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, subject worksheets).
In general, CRFs may not serve as source documents, aside from the data elements listed below. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents. Data reported on the CRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by an Investigator and filed in the subject's research records at the site.

The investigator must ensure the availability of source documents from which the information on the CRFs was derived. The type and location of source documents should be documented. 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.

The CRF may be considered source for the following data collection elements:

- Study Assignment CRF
  - Target vein assignments
- Procedure General CRF
  - Number of VenaSeal treatments completed by treating physician to date
  - VenaSeal kit usage: Product number, lot number, and why the kit was utilized
  - Physician satisfaction with procedure
  - Would the treating physician have preferred to use a secondary therapy
- AE CRF
  - Date study site became aware of event
  - Procedure relatedness and device relatedness
- DD CRF
  - Date study site became aware of event
  - DD led to Serious adverse device event (SADE)
- Subject Death
  - Date study site became aware of death
- Deviations
  - Reason for deviation.

10.16. Deviation Handling

A CIP and/or study deviation is defined as an event where the investigator or investigational site personnel did not conduct the clinical study according to the clinical investigation plan or CTA. Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one case report form.

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 IRB/EC/CA within time period required by the regulations and reported to Medtronic as well. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide study site-specific reports to investigators summarizing information on deviations that occurred at the investigational study site on a periodic basis.

Examples of CIP deviations include but are not limited to the following:

1. Failure to obtain informed consent from patient prior to study participation.
2. Incorrect version of the ICF used.
3. Failure to obtain IRB/EC approval and CA approval, if applicable, before the start of the study.
4. Treated subject did not meet inclusion/exclusion criteria.
5. Subject not treated per the treatment assigned by randomization.
6. Required assessment(s) during visit not done.
7. Subject failure to attend a follow-up visit
8. Adjunctive therapy visits occurring prior to 3 months post-index procedure for subjects assigned to ETA and VenaSeal™ treatment arm. For subjects in the surgical stripping arm, any additional adjunctive therapy occurring (excluding the adjunctive treatment completed along with the index procedure) prior to 3 months.
9. Subject attends a follow-up visit which occurred outside the visit window (data is still to be entered in the CRF of the applicable visit).
10. AEs and device deficiencies not reported in the required time to Medtronic or the EC/IRB in the frame as required by regulation or as specified in the CIP (according to section 12.3).
11. Source data permanently lost.
12. Enrollment of patients during lapse of IRB/EC approval and CA, if applicable.
13. Enrollment limits exceeded.

Investigators may not deviate from the CIP and waivers cannot be used for this study, unless the deviation is necessary to protect the rights, safety and wellbeing of the subject in an emergency situation. Deviations should be reported to Medtronic regardless of whether medically justifiable or taken to protect the subject in an emergency. Study deviations should be reported to Medtronic via the study deviation CRF.

Investigators are required to adhere to local IRB/EC procedures and CA procedures (if applicable) for reporting deviations. In addition, investigators should report the following deviations to Medtronic and their reviewing IRB/EC and CA (as applicable) without any delay (per the timelines required by IRB/EC/CA):

- Failure to obtain written informed consent.
- Deviations to protect the life or physical well-being of a subject in an emergency.

10.17. Subject Exit, Withdrawal or Discontinuation

10.17.1. Study Exit

A study exit CRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject death
- Screen Failure
- Subject didn't receive treatment for any of the target vein
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, failure of subject to maintain adequate study compliance).

The following information is required to be collected at study exit:

- Date of the exit
- Reason for exit.

If discontinuation is because of safety, the subject may be asked to be followed for collecting safety data outside the clinical investigation.

10.17.2. Study Completed

The study will be considered completed when the last subject is exited and the database is locked. The 60 months follow-up visit and exit visit should be combined, as applicable and both CRFs need to be completed. The subject will continue to be followed as per standard of care after study completion and no specific assessments are needed post study completion. VenaSeal vs. Surgical Stripping Study subjects will be exited following the 12 month visit.

10.17.3. Lost to Follow-up

The study site will make every effort to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful and the site should contact the study team before exiting the subject. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone and if contact via phone is not successful, a traceable letter from the investigator should be sent to the subject's last known address, a copy of which should be maintained in the subject's study record. All contact efforts to obtain follow-up must be documented in the subject's medical records.

10.17.4. Subject Chooses to Exit (i.e. Revokes Consent)

A study subject has the right to discontinue participation in the study at any time without penalty or loss of benefits to which the subject is otherwise entitled. A withdrawn subject will be treated according to standard of medical care and will not be replaced. If the subject no longer wants to participate in the study, no further personal data will be collected. Subjects will be included in the analyses up to the time that consent was withdrawn. The subject can also withdraw the consent to process the personal data. In that case, Medtronic may not delete the data to comply with legal obligations (such as storage periods) and/or to the extent that processing these data is necessary to ensure the validity of the study results.

If the subject decides to withdraw from the study, the investigator will document the reason for withdrawal, if known, and indicate any rationale for the withdrawal from the study in the subject's file and a Study Exit CRF must be completed. If a subject is withdrawn from the study due to problems related to the device or for safety reason, permission may be requested to follow up with the subject outside of the study due to withdrawal based on problems related to the safety or device performance. The site shall request permission from the subject to collect safety data up to 30 days from the day of exit (Safety data can be collected during the 30 days visit in-hospital or by phone as deemed appropriate by Investigator. Follow-up of any ongoing events will be done according to normal hospital practice and in accordance with local requirements). In all other cases, no additional data will be captured after the subject withdraws or is removed from the study, unless the information is publicly available. Subjects have the right to withdraw from the study at any time without explaining why and without any consequences.

10.17.5. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If the subject was randomized, it is preferred to keep the subject in the study and perform study

procedures/collect data to the extent possible. If an Investigator withdrawal is necessary, the reason for subject withdrawal should be collected prior to subject withdrawal if possible.

10.17.6. Conditional Disengagement

After a subject is enrolled/randomized every effort should be made to keep the subject in the study. However, it is recognized that there are circumstances where limited data may be collected, or study exit will need to occur. In these cases, we will consider either modified data collection requirements where subjects may conditionally disengage in study procedures but data from the subject can still be collected because the subject has not revoked consent or exit when study participation is completely ended. In randomized subjects, modified data collection is always preferred over exit.

Subjects may be conditionally disengaged from study procedures for any of the following reasons:

- Subject chooses to disengage (e.g., follow-up schedule cannot be adhered to, study burden too large, relocation to another geographic location).
- Investigator deems conditional disengagement necessary (e.g., medically justified).

If the subject wishes to disengage from the study, or the investigator deems it necessary, the study site is required to document the reason. Prior approval from the study team is required and a Limited Data Collection CRF needs to be completed. Data collection requirements no longer apply, but study sites are encouraged to collect as much data as possible on the regular CRFs.

11. Risks and Benefits

11.1 Potential Risks

This study assesses the use of the VenaSeal™ Closure Device in comparison with surgical stripping or ETA treatment. The risk analysis process for the VenaSeal Spectrum study is being performed in accordance with ISO 14971 and will ensure that the level of risk is acceptable prior to starting the study. None of the treatment devices, materials, and techniques related to standard diagnostic and treatment procedures will be changed in this study. The device designs used in this study are commercially available and have a proven safety record. Standard risks associated with medical devices used in this study and risks associated with superficial venous disease treatment procedures are provided in the respective device IFUs. Additional risks, which are not known at this time, may also exist. In addition, the study design will minimize the risks through center and investigator selection criteria, careful subject selection and management, adherence to the schedule of assessments and adverse event monitoring.

11.2. Potential Risks of the Procedure

Below are a list of the potential adverse effects and additional precautions associated with the use of the VenaSeal™ closure system, according to the IFU at time of protocol finalization. Potential AEs that may be associated with the VenaSeal™ closure system are similar to those associated with other endovenous treatments that close the diseased vein. Please refer to the respective IFU as applicable per region for current and applicable information.

The potential AEs (e.g., complications) associated with the use of the VenaSeal™ system include, but are not limited to, the following list:

- Arteriovenous fistula
- Bleeding from the access site
- Deep Vein Thrombosis (DVT)
- Edema in the treated leg
- Embolization, including PE
- Foreign body reactions (including, but not limited to, hypersensitivity or allergic reactions to cyanoacrylates, such as hives, asthma, anaphylactic shock, and nonspecific inflammation of the cutaneous and subcutaneous tissue)
- Hematoma
- Hyperpigmentation
- Infection at the access site
- Pain
- Paresthesia
- Phlebitis
- Superficial thrombophlebitis
- Urticaria or ulceration may occur at the injection site
- Vascular rupture and perforation
- Visible scarring.

Additional Precautions for the VenaSeal™ Closure System:

- The safety and effectiveness of the VenaSeal™ system in pregnant women and in pediatric patients have not been established.
- The VenaSeal™ system is sterile unless the package is opened or damaged. The package should be examined prior to use. If the package is damaged DO NOT USE.
- The VenaSeal™ system is intended for single patient use only. DO NOT REUSE or RE-STERILIZE.

- Prior to use, carefully examine the VenaSeal™ system components and verify they, and their packaging, have not been damaged during shipment. If the components show any sign of damage DO NOT USE.
- Do not use after the expiration date.
- Verify that the VenaSeal™ adhesive is a clear and free-flowing liquid prior to use. Material that is discolored should be discarded.
- The VenaSeal™ adhesive will adhere to most surfaces. Avoid contact with non-disposable surfaces.
- Gloves and eye/face protection are recommended when handling the VenaSeal™ adhesive.
- The VenaSeal™ adhesive is intended to be delivered via the VenaSeal™ delivery system components only.

11.3. Risk Minimization

The potential risks associated with the therapies in this study were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP.

In addition, investigators will be actively involved in the treatment and follow-up of the subjects treated with the study therapies.

Risks will be minimized by careful assessment of each subject prior to, during, and after treatment with any of the study therapies.

The products used for this study are the devices that are approved in the regions they are used. Medtronic has further minimized the possibility of risks by implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

After treatment, subjects in the VenaSeal Spectrum study will be followed at regular intervals to monitor their condition following the therapy. At each protocol required follow-up, the investigator must assess any adverse events.

11.4. Potential Benefits

Surgical stripping has long been the gold standard for successful removal of incompetent varicose truncal veins. ETA is a minimally invasive method that uses thermal ablation, either through radiofrequency or laser, for closure of incompetent varicose truncal veins. The VenaSeal™ closure system is also a minimally invasive method and provides vein closure through injection of cyanoacrylate glue without the

administration of heat. Improvements from treatment include reduction in rVCSS and AVVQ scores at follow-ups from 1 week to 36 months.[27] All three treatments have high rates of closure and lead to clinical improvement.

11.5. Risk-Benefit Rationale

The probable benefits of the VenaSeal™ closure system are based on outcomes reported in the VeClose Pivotal IDE study as well as the Feasibility and eSCOPE studies described in section 4.1, Background. These data were used to support regulatory approval of the VenaSeal™ system. The use of the VenaSeal™ system to treat VRD in the GSV, a superficial truncal vein, resulted in high closure rates, and these results are consistent with the reported closure success rates with ETA treatments (i.e., RFA, EVLA). In addition, the VenaSeal™ system addresses some challenges associated with current ETA technologies such as less bruising (ecchymosis) and rapid return to normal activities without the need for compression stockings following treatment.[33,34] The risks are similar to RFA, which is currently a commonly-used and comparative treatment modality that will be allowed as part of the ETA arm in this study.

Regarding study participation, subjects are not put at any additional risk for participating in the study, as compared to being treated with the VenaSeal™ system, through ETA, or a surgical stripping treatment as part of their routine care. Subjects for whom it is unethical to be randomized to one of the treatment arms, should not be included in this study. Subjects who are included in this study will receive an increased level of care from their physicians as a result of participation, specifically additional follow-up visits and AE assessments.

Given the available information above, the data support that for use in the treatment of lower extremity symptomatic varicose veins, the probable benefits of treatment with the VenaSeal™ system, treatment with ETA, or treatment through a surgical stripping procedure outweigh the probable risks.

12. Adverse Events and Device Deficiencies

12.1. Definitions/Classifications

12.1.1. Definitions

For the purposes of the clinical report, Medtronic will classify each AE and device deficiency according to ISO 14155:2020 where applicable **(Table 10).** Where the definition indicates “device” for the VenaSeal™ system, it refers to any component of the VenaSeal™ closure system used in the study. Surgical instruments used as part of the surgical stripping or ETA procedures other than Medtronic’s ClosureFast™ device will not be considered for device deficiency assessment.

In situations where country-specific definitions and safety reporting regulations are stricter than those mandated per ISO14155:2020, reporting will be performed in compliance with the country-specific safety regulations.

Table 10: Adverse Event and Device Deficiency Definitions

Adverse Event (AE): **(ISO 14155:2020 3.2)** 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 and whether anticipated or unanticipated. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.
Adverse Device Effect (ADE): **(ISO 14155:2020 3.1)** AE related to the use of an investigational medical device. NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from user error or from intentional misuse of the investigational medical device. NOTE 3: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE): **(ISO 14155:2020 3.45)** <u>AE that led to any of the following</u> a) death, b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function including chronic disease, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

Serious Adverse Device Effect (SADE): **(ISO 14155:2020 3.44)**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device deficiency (DD): **(ISO 14155:2020 3.19)**

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

NOTE 1: DD include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
NOTE 2: This definition includes DD related to the investigational medical device or the comparator.

Unanticipated Serious Adverse Device Effect (USADE) ***(ISO 14155:2020 section 3.51)***

SADE which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Serious Health Threat ***(ISO 14155:2020, 3.46)***

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

SAE definition and reporting in Germany will be in conformance with Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten (Medizinprodukte-Sicherheitsplanverordnung- MPSV) and with the rules of the electronic reporting procedures published on the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) homepage.

Serious Adverse Event (SAE) definition: (MPSV § 2 Definitions Abs 5)
In accordance with this regulation –
A serious adverse event (SAE) is an event that occurs in a clinical investigation subject to approval or occurring in a performance evaluation which led, might have led or could lead directly or indirectly to death or serious deterioration of health of the subject, the user or a third party, without consideration if the event has been caused by the medical device itself; this applies accordingly to serious adverse events occurring in a clinical investigation or performance evaluation.

An event is not considered an AE if it has been identified as a pre-existing condition, unless there is a change in nature, severity or degree of incidence of the event.

12.1.2. Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the study device (for VenaSeal™ and ETA treatment only) and index-procedure will be classified as not related, unlikely, possible, probable or causal relationship **(Table 11).**

Table 11: Causality Assessment

Not related	Relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

	• the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal relationship	The event is associated with the investigational device or with procedures beyond reasonable doubt when:
	• the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• the event has a temporal relationship with investigational device use/application or procedures;
	  ○ the event involves a body-site or organ that
	  ▪ the investigational device or procedures are applied to;
	  ▪ the investigational device or procedures have an effect on:
	  ○ the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
	• the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
	• other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
	• harm to the subject is due to error in use;

	• the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The following definitions **(Table 12)** are intended as guidelines for classifying causal relationships between the event and the VenaSeal™ or ETA system and the index- procedure (Timeframe for assessing implant procedure relationships begins when subject is being prepared for the procedure).

Table 12: Adverse Event Relationship Definitions

Related to	Definition
Procedure with the VenaSeal™ closure system, ETA, or surgical stripping (procedure relatedness)	Any AE that occurs within 30 days of the index procedure unless specifically shown not to be related to that procedure.
VenaSeal™ closure system (product relatedness)	Any AE involving the function of the product, or the presence of the product in the body. Included in this category are events that are directly attributed to the product.
ETA devices (product relatedness)	Any AE involving the function of the laser or RF generator used in a treatment with the ETA arm. Included in this category are events that are directly attributed to the product.

12.2. Foreseeable Adverse Events and Foreseeable Adverse Device Effects

A list of adverse events or complications associated with the use of the applicable devices that may occur or require intervention can be found in the applicable IFU. These expected events are considered anticipated adverse events that can be predicted to occur with some frequency, irrespective of how low that frequency is expected to be. For the list of anticipated AEs and anticipated adverse device effects associated with the treatments in this study refer to the applicable IFUs.

Medical occurrences that are inherent to an intervention and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include those listed in **Table 13**. These medical occurrences should not be reported as AEs during this study.

12.3. Recording and Reporting of Adverse Events

Events will be recorded on the appropriate CRFs entering information as documented in the subject's medical records. Events will be reported throughout the course of study (from the moment the index procedure is initiated until completion of follow up or exit). Due to the post market nature of this study, only adverse events meeting the below criteria will be reported).

1. All AEs occurring in the target limb, including but not limited to the following specific events:
    - Hypersensitivity
    - Phlebitis
    - Granuloma
    - Endovenous glue induced thrombosis (EGIT) or endovenous heat induced thrombosis (EHIT)
    - Symptomatic DVT.
2. Symptomatic PEs
3. Serious adverse events (SAE)
4. Non-subject (users) adverse events: AEs occurring to the users or other site personnel related to the device or the procedure.

For all reportable AEs, investigators should assess and record at least the following information on the AE CRF:

1. Date the event started (if full date is not available, partial date is allowed)
2. Date site became aware of event
3. Date event first determined to be a Serious Adverse Event, if applicable
4. Event term
5. Event description
6. Action taken/treatment
7. Which seriousness criteria did the event meet, if applicable
8. Relationship of the event to the procedure
9. Relationship of the event to the device (for VenaSeal™ and ETA treatment only)
10. Narrative (describe any additional details relevant to the AE)
11. Outcome of the event.

Events described in **Table 13** are considered unavoidable events inherent to surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion Unavoidable events should not be reported unless the event worsens or is present outside the stated timeframe from the index procedure.

Table 13: Expected and Unavoidable not to be reported adverse events

Event Description	Timeframe from the procedure
Anesthesia related nausea/vomiting	24 hours
Low-grade fever (<100°F or <37.8°C)	48 hours
Incisional pain (with or without standard treatment and patient not returning to clinic to have additional treatment)	72 hours
Mild to moderate bruising / ecchymosis *	7 days
Back pain related to laying on table	72 hours

Bleeding at access site (not requiring treatment)	24 hours
Emergency room visits and procedures not meeting the SAE definition**	NA

* Ecchymosis events will not be considered AEs unless they are classified as significant by the Investigator due to the more serious nature of it.

**Emergency room visits and procedures will not be considered collectable AEs unless there is a potential relationship with the VenaSeal™ system.

12.4. Recording and Reporting of Device Deficiencies

Device deficiency information will be collected and recorded throughout the study. The Device Deficiencies related to the VenaSeal™ system and Medtronic ClosureFast™ system (ETA treatment modality) will need to be reported in the CRF.

- Device deficiencies that lead to an AE by study definition will be reported on the AE CRF only.
- Device deficiencies that did not lead to an AE will be reported on a Device Deficiency CRF (one for each device deficiency).
- Device deficiencies that did not lead to an AE but might have led to a 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 on a Device Deficiency CRF.
- Device deficiencies that did not meet any of the above criteria will be reported to Medtronic through normal complaint process.

The Device Deficiencies related to any other products used in the study should be reported per site's standard practice of reporting to their manufacturer. This reporting requirement is a deviation from ISO 14155:2020 due to the post-market nature of the study.

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. In addition to study requirements outlined above, additional reporting of product complaints by the site must be done according to the local Standard Operating Procedures. Medtronic will notify the Regulatory Authority (e.g., CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury.
  - Permanent impairment of a body function or permanent damage to a body structure.
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

12.5. Adverse Event and Device Deficiency Review Process

AEs/Device Deficiencies will be reviewed by Medtronic Study Management and/ or designee. This review will include the determination whether the AE/Device Deficiency meets regulatory reporting requirements. The sponsor will ensure timely AE/Device Deficiency reporting to meet global and country specific regulatory requirements.

12.6. Reporting of Adverse Events

The information below outlines the AE reporting requirements from the investigator to Medtronic (**Table 14).** Investigators and Medtronic are obligated to report AEs to their EC/IRB in accordance with the requirements and local regulations. Refer to section 12.3 and section 12.4 for a list of types of AEs that are required to be reported during the study.

Table 14: Investigator reporting requirements

Timeframe for Reporting	Event Type
Immediately, but no later than 3 calendar days 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. Device Deficiency (DD). • Device Deficiency that might have led to a SADE • Serious Adverse Device Effect (SADE) • Serious Adverse Event (SAE)
In a timely manner from the investigator's / site's first knowledge of the event	Adverse Event (AE): only those that are required to be reported according to CIP.

12.7. Emergency Contact for Reporting Events and Device Deficiencies

Investigators should contact their Medtronic clinical representative if they have any questions regarding AEs and/or device deficiencies. Sponsor contact information is subject to change and will be maintained in a document separate from the clinical investigation plan and provided to sites.

If the CRF is not available for immediate recording, the paper AE or Device Deficiency Form in the ISF must be completed and submitted to the email box specified in the ISF and to the Medtronic clinical study monitor. In due time, the AE or device deficiency needs to be entered in the CRF as well.

12.8. Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.
In the event that a subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved procedure related AEs, as classified by the investigator, are resolved or unresolved with no further actions planned. Additionally, if there are procedure related AEs at the time of study completion, the subject should not be exited, but should continue to be followed for up to 30 days to assess the ongoing AE. Once the ongoing system or procedure AE(s) is/are resolved, or the subject has been followed for 30 days whichever occurs first, the subject should be exited. If AEs are still ongoing 30 days post study completion, it should be noted on the AE CRF that the AE is unresolved at time of study exit.
At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.9. Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one AE with the outcome of death.
A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if

available and allowed by state/local law. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death.
In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law).

13. Data Review Committees

13.1. Clinical Events Committee (CEC)

A Clinical Events Committee will provide independent medical review and adjudication of AE data. The CEC will adjudicate only the safety endpoint events specified in the CEC Charter reported by the investigators. Source documents to support adjudication may be requested. Further AEs may be reviewed and adjudicated upon request of the sponsor. The CEC will follow the definitions for classifying AEs that relate to clinical safety endpoints as described in the CEC Charter.

The CEC members will be free from bias towards the study and will be independent from the study investigators, Medtronic and regulatory authorities. The committee will consist of experts (non-Medtronic employed physicians) with training or experience relevant to the study.

Events for all three Studies requiring at minimum adjudication include the following through 12 months post-index procedure:

1. Specific target limb adverse events (AEs):
    - Hypersensitivity to VenaSeal™ adhesive
    - Phlebitis
    - Granuloma
    - EGIT or EHIT

In addition, any Serious Adverse Events (SAEs) will be adjudicated through 12 months post-index procedure.

The CEC will be established and led by:

NAMSA (previously Syntactx)
150 Greenwich Street
Floor 44
New York, NY 10007

13.2. Lead Principal Investigators

The lead principal investigators will take responsibility for the scientific validity of the clinical investigation plan, assessment of the study quality and conduct as well as for the scientific quality of the data analysis and reporting.

13.3. Ulcer Assessment Core Laboratory

The ulcer assessment core laboratory is responsible for assessing target limb VLU size, healing, recurrence and other applicable measurements. VLU photographs and select data points (e.g., ulcer origin date, date of visit) will be provided to the core laboratory by designated VLU Study sites through imaging systems provided to the site by the ulcer core laboratory. The core laboratory will report all ulcer data to Medtronic per a standardized process. Additional details are available under separate cover.

The ulcer assessment core laboratory will be established and led by:

Syntropic Core Lab
3545 Olentangy River Rd #514 |
Columbus, OH 43214 |
Office: 614-788-5830

14. Statistical Design and Methods

This evaluation has been designed as a global, post-market, prospective, multi-center, randomized controlled study of patients with symptomatic superficial venous disease, with a single arm embedded ulcer study. The study is designed with two Randomized Studies (VenaSeal vs. Surgical Stripping Study and VenaSeal vs. ETA Study) for CEAP 2-5 subjects and one single arm active VLU Study with CEAP 6 subjects. Each study will be individually assessed and analyzed for the overall study objectives.

The three primary endpoints in the Randomized Studies will be measured to compare VenaSeal vs. the treatment of ETA or surgical stripping on VenousTSQe and VenousTSQs (separately) at 30 days, and elimination of clinically relevant superficial truncal disease in the target vein at the time of index

procedure. The primary endpoint of the VLU Study is time to ulcer healing and will be measured until healing has occurred.

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods used to analyze the study objectives. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

All statistical analyses will be performed using Statistical Analysis System (SAS) software (version 9.2 or higher) or other widely accepted statistical or graphical software.

Statistical analysis methods are discussed separately for the Randomized Studies and the single-arm VLU Study below.

14.1. Randomized Studies

Analyses will be performed on all patients who pass the point of enrollment (randomization), according to the intention-to-treat (ITT) principle. Patients will be analyzed in the arm they are randomized to regardless of the treatment received. There are three primary endpoints and two key secondary endpoints with formal hypothesis testing for the Randomized Studies. Multiplicity adjustment needs to be considered to control the overall type I error. Each randomized study will have a family-wise type I error rate of 0.05. Within each study, a Hochberg procedure (Benjamini & Hochberg, 1995) will be used to control the family-wise type I error rate to 0.05 for the primary endpoints. Type I error preserved from the primary endpoints will be used for the key secondary endpoints.

A type I error of 0.0167 will be used in the following sample size calculations for this purpose.

In the two Randomized Studies, three primary endpoints will be assessed: 1) Peri-procedural patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days; 2) Patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days, and 3) elimination of clinically relevant superficial truncal disease in each target vein at index procedure. The two key secondary endpoints include achieving the anatomical closure of superficial truncal veins at 6 months and the ability to return to work post-index procedure.

For VenaSeal vs Surgical Stripping Study, 108 patients randomized before 22-Feb- 2022 will be included in the analysis. These patients will be followed for 12 months after index procedure. Since the enrollment was stopped for VenaSeal vs. Surgical Stripping Study with up to 108 subjects, there is still reasonable

power for the two TSQs and key secondary objectives. Therefore, the VenaSeal vs Surgical Stripping Study will test two primary endpoints (Venous TSQe and TSQs at 30 days) and key secondary endpoints. The elimination of truncal reflux at the index procedure will be summarized but not tested for hypothesis testing.

14.1.1. Sample Size Evaluation on Primary Endpoints

VenousTSQ

Subject experience and satisfaction will be measured through a new, patient-centered venous treatment satisfaction questionnaire (VenousTSQ). The VenousTSQ is designed to have two components, the VenousTSQe and the VenousTSQs. As a result of the different content of both components of the VenousTSQ, the related endpoints are split into two separate primary endpoints, being:

1. Peri-procedural patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days.
2. Patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days.

While the VenousTSQ is a newly-developed PROM and its scoring guidelines are currently under development at the time of finalization of this protocol, the final versions of the questionnaires provide sufficient insight in the eventual scoring scales. Each of the two parts consists of 8-11 items in total. VenousTSQe consists of 8 items (13 including sub-items) with items being able to be scored with yes/no or from 6 – 0. VenousTSQs consists of 11 items (15 including sub-items) and items can similarly be scored with yes/no or from 6 – 0. Consequently, VenousTSQe and Venous TSQs have a potential scale that range runs from 0 - 78 and 0 – 90, respectively. Final scoring guidelines will be evaluated via psychometric analysis utilizing data from approximately 100 English-speaking enrolled patients. Sample sizes are provided in **Table 15** for different scenarios with a varying final scoring.

To determine the variance (SD), a comparison was made to other treatment satisfaction questionnaires (TSQs) that were developed by the same expert group. The Macular TSQ (MacTSQ) was designed as a measure of patient satisfaction with treatment for macular disease. The questionnaire consists of two subscales with each a maximum score of 36 (6 questions each) and a single scale with a maximum score of 72 (12 questions). The SD was reported as 3.56 for subscale 1, 5.04 for subscale 2, and 7.30 for the single scale[35]. The Diabetes TSQ (DTSQ) was designed as a measure of patient satisfaction with treatment for diabetes. The questionnaire consists of a scale with a maximum score of 48 (8 questions) and a typical SD is around 5.0[36,37]. To determine the SD for the two VenousTSQ endpoints, an overestimate was made in comparison with literature findings. As such, the SD was selected to be 10 for VenousTSQe and VenousTSQs endpoints, respectively.

The null hypothesis on the primary endpoints of VenousTSQe and VenousTSQs at 30 days is that the VenaSeal™ system arm will have same PROM scale as that of the control (ETA or surgical stripping) arm. The alternative hypothesis is that the VenaSeal™ system arm will have a different PROM scale from that of the control arm. Rejection of the null hypothesis in favor of the VenaSeal™ system will signify that the treatment satisfaction with the VenaSeal™ system is superior to the treatment with ETA or surgical stripping. A minimum difference of 0.5 points per item, as a total score, is utilized as the minimum meaningful difference between comparison groups.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $p_A = p_C$

Ha: $p_A \neq p_C$

Where p_A and p_C are the true PROM scale for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively.

The parameter assumptions are:

- $p_A - p_C$ =4 and 5.5 PROM points for VenousTSQe and VenousTSQs, respectively
- Common standard deviation of 8 and 11 PROM points for VenousTSQe and VenousTSQs, respectively
- T test with two sided α 0.0167
- 1:1 randomization
- 7% attrition rate for VenousTSQ at 30 days

With these assumptions, a total of 237 subjects (220 evaluable, 110 in each arm) will yield 90% power to reject the null hypothesis in favor of the alternative hypothesis of superiority on VenousTSQe and VenousTSQs at 30 days, in each study.

Assuming the standard deviation increases with the number of questions and the minimum clinical difference of 0.5 points per question, the sample size calculations are not impacted by the number of questions. Therefore, sample size adjustments are not anticipated if the number of questions varies from 8 or 11.

Table 15: VenousTSQ Sample Size Evaluation

Number of Venous TSQ questions	Difference of PROM Points	SD of PROM points (assuming equal in both arms)	Sample size (1:1 evaluable)
6	3	6	110:110
8	4	8	110:110
10	5	10	110:110
11	5.5	11	110:110
12	6	12	110:110

Elimination of truncal reflux

The third primary endpoint is the elimination of clinically relevant superficial truncal disease in target veins at the index procedure. This endpoint will be measured as a percentage of treated vein vs. diseased vein for each target vein.

Based on clinical experience, the minimal clinically relevant difference in mean percentage of truncal disease elimination between treatment modalities is expected to be 10%. To calculate the sample size, a combination of the smallest minimal clinically relevant difference and the largest variance (SD) are justified being the conservative assumptions. An SD of 20% was estimated as being the maximum likely seen and is therefore used to calculate the sample sizes.

The null hypothesis on this primary endpoint is that the VenaSeal™ system arm will have the same percentage of reflux eliminated at the index procedure as that of the control (ETA or surgical stripping) arm. The alternative hypothesis is that the VenaSeal™ system arm will have a different percentage of reflux eliminated at the index procedure from the control arm. Rejection of the null hypothesis will signify that the treatment with the VenaSeal™ system is superior to the treatment with ETA or surgical stripping.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $\mu_A = \mu_C$
Ha: $\mu_A \neq \mu_C$

Where μ_A and μ_C are the true percentage of reflux treated at the index procedure for the VenaSeal™ system arm and ETA or surgical stripping arm.

The parameter assumptions are:

- μ_a μ_C = 10%
- Common standard deviation of 20%
- Two-sided t test with α = 0.0167
- 1:1 randomization
- 3% attrition

With these assumptions, a total of 227 subjects (220 evaluable, 110 in each arm) will yield 90% power to reject the null hypothesis in each study.

14.1.2. Sample size evaluation on key secondary endpoints

Return to work

Return to work is defined as the time in days patients need following a procedure to return to work. Return to work time can be influenced by factors that are independent of the type of work they are employed to do (e.g., including physical effort), the type of anesthesia that is used with or without hospitalization, and other regional/cultural differences.

To minimize the effects of independent factors that may influence the return to work time, several measures will be taken into account. Employment status will be captured for all patients. Only patients who have an active employment status (employed or independent worker, including stay at home parents) will be included in the analysis for return to work time. Information will be captured on the category of occupation to be able to distinguish between physical and sedentary work. The analysis may correct for weekends and part-time work as applicable.

A literature search on historical data for return to work time following treatment of venous reflux disease was conducted using the PubMed database of clinical literature. Publications describing return to work times for treatment of venous reflux disease with the VenaSeal™ closure device, any type of endovenous laser ablation and radiofrequency ablation, or surgical stripping were considered.

The resulting return to work times are summarized in **Table 16.** Where applicable, the return to normal activities time is included. The corresponding sample size (based on ITT) and measure of return time (mean vs. median) are included in the table. The results of the first five rows were used to estimate sample sizes for the return to work endpoint because these studies specifically report the mean and SD. Using a conservative approach, the resulting SDs for the three treatment groups (ETA, VenaSeal™ treatment, and surgical stripping) were compared against the median and IQR of the remaining findings to make sure the used estimations were justified compared to existing data. With this approach, the smallest differences between treatment with the VenaSeal™ device and the other treatments are utilized to calculate the final sample size.

Table 16: Return to work/normal activity time post treatment

AUTHOR	YEAR	TREATMENT TYPE	SAMPLE SIZE (# PTS, ITT)	MEASURE	TIME IN DAYS TO RETURN TO NORMAL ACTIVITIES	TIME IN DAYS TO RETURN TO WORK
PRONK	2010	ETA: Laser	62	Mean (SD)	3.2 (4.3)	4.4 (5.4)
LURIE	2003	ETA: RFA	45	Mean (95% CI)	1.15 (0.05-2.34)	4.7 (1.16-8.17)
GIBSON	2017	VenaSeal™	50	Mean (SD)	2.4 (+/- 4.1)	0.2 (+/- 1.1)
LURIE	2003	Surgical stripping	40	Mean (95% CI)	3.89 (2.67-5.12)	12.4 (8.66-16.23)
PRONK	2010	Surgical stripping	68	Mean (SD)	3.2 (4.0)	4.2 (3.7)
SAMUEL	2013	ETA: Laser	38	Median (IQR)	4 (1-14)	4 (0-12)
	2013	ETA: Laser	38	Median (IQR)	3 (1-14)	3 (1-8)
RASMUSSEN	2011	ETA: Laser	125	Median (range)	2 (0–25)	3.6 (0–46)
COTTON	2016	ETA: Laser	212	Median		7.7
LATTIMER	2012	ETA: Laser	56	Median (IQR)	7.5 (2-15)	
CARRADICE	2011	ETA: Laser	140	Median (IQR)	3 (1-10)	4 (2-14)
RASMUSSEN	2011	ETA: RFA	125	Median (range)	1 (0–30)	2.9 0–14)
LANE	2016	ETA: RFA	83	Median (IQR)	2 (1-7)	2 (2-7)
SUBRAMONIA	2010	ETA: RFA	48	Median (IQR)	3 (2-5)	10 (4-13)
CHAN	2017	VenaSeal™	29	Median (range)		1 (1-16)

The null hypothesis for the key secondary endpoint is that the VenaSeal™ system arm will have the same days to return to work as that of the control (ETA or surgical stripping) arm. The alternative hypothesis is that the VenaSeal™ system arm will have different days to return to work than that of the control arm. Rejection of the null hypothesis in favor of VenaSeal will signify that the ability to return to work after treatment with the VenaSeal™ system is superior to ETA or surgical stripping.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $r_A = r_C$
Ha: $r_A \neq r_C$

Where r_A and r_C are the true days to return work for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively.

The parameter assumptions are:

- rA = 0.2 in the VenaSeal™ system arm and rC = mean 3 and 8 in ETA arm and surgical stripping arm, respectively
- standard deviation of 1.1 in the VenaSeal™ system arm, 2 in ETA arm and 3 in surgical stripping arm
- Two-sided t test with □ = 0.0167
- 1:1 randomization.

With these assumptions, a total of 22 subjects (evaluable; 11 in each arm) in the VenaSeal vs ETA Study and 10 subjects (evaluable; 5 in each arm) in Surgical Stripping Study will yield 90% power to reject the null hypothesis in favor of the alternative hypothesis of superiority in each study.

Closure rate

Closure rate is a generally used measure to determine the short and long-term success of venous reflux disease treatment. Literature may report on closure rate, occlusion rate, or recanalization rate at various moments in time. The endpoint used in this study focuses on the closure rate measured at 6 months.

To calculate the sample size based on historical data on closure rate, a literature search was conducted using the PubMed database of clinical literature. Any literature older than 10 years was excluded from the analysis. Six-month closure rates for treatment of venous reflux disease with the VenaSeal™ closure device, any type of endovenous laser ablation and radiofrequency ablation, or surgical stripping were considered.

Closure rates were weighted within a treatment arm by multiplying the closure rate for that treatment with the sample size of the treatment arm. **Table 17** shows an overview of the literature that was used to calculate weighted closure rates that were used for sample size calculations.

Table 17: Closure rates for treatment of venous reflux disease

AUTHOR	YEAR	TREATMENT	FOLLOW-UP	SAMPLE SIZE (# PTS, ITT)	CLOSURE/OCCLUSION RATE
BRITTENDEN	2015	ETA: Laser	6M	212	83.0%
BOZOGLAN	2016	ETA: Laser	6M	60	100.0%
EROGLU	2018	ETA: Laser	6M	175	95.1%
SYDNOR	2017	ETA: Laser	6M	100	100%
WOZNIAK	2016	ETA: Laser	6M	56	100%
MESE	2015	ETA: Laser	6M	60	100%
ATASOY	2015	ETA: Laser	6M	44	100%
CALIK	2019	ETA: Laser	6M	200	95.6%
LANE	2016	ETA: RFA	6M	82	93.0%
BETELI	2017	ETA: RFA	6M	43	95.3%

AUTHOR	YEAR	TREATMENT	FOLLOW-UP	SAMPLE SIZE (# PTS, ITT)	CLOSURE/OCCLUSION RATE
EROGLU	2018	ETA: RFA	6M	175	94.1%
SYDNOR	2017	ETA: RFA	6M	100	97.3%
MENDES	2016	ETA: RFA	6M	18	80.0%
WOZNIAK	2016	ETA: RFA	6M	54	100%
MESE	2015	ETA: RFA	6M	60	95.0%
YANG	2013	ETA: RFA	6M	100	99.0%
MORRISON	2018	ETA: RFA	6M	114	96.2%
CRETON	2010	ETA: RFA	6M	295	98.6%
CHAN	2017	VenaSeal™	6M	57	90.3%
ALMEIDA	2013	VenaSeal™	6M	38	92.1%
GIBSON	2016	Venaseal™	6M	70	98.0%
PROEBSTLE	2015	VenaSeal™	6M	70	91.4%
MORRISON	2018	VenaSeal™	6M	108	99.0%
BRITTENDEN	2015	Surgical stripping	6M	294	84.4%
JIA	2010	Surgical stripping	6M	26	89.5%

Table 18 shows an overview of the weighted average closure rates at 6 months that were used to calculate the sample size for this endpoint.

Table 18: Weighted Average Closure Rate

COMPARATOR	TOTAL NUMBER OF CONSIDERED STUDIES	TOTAL SAMPLE SIZE IN CONSIDERED STUDIES	WEIGHTED AVERAGE CLOSURE RATE AT 6M
VENASEAL™	5	343	95.0%
ETA	14	1948	95.4%
SURGICAL STRIPPING	2	320	84.8%

The null hypothesis on this key secondary endpoint is that the closure rate at 6 months in the VenaSeal™ system arm will have less than or equal to that in the control (ETA or surgical stripping) arm minus a clinically relevant difference of 10%. The alternative hypothesis is that the closure rate at 6 months in the VenaSeal™ system arm will be greater than that in the control arm minus a clinically relevant difference of 10%. Rejection of the null hypothesis will signify that the treatment with the VenaSeal™ system is not inferior to the treatment with ETA or surgical stripping.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $\pi_A \leq \pi_C$ - 10%
Ha: $\pi_A > \pi_C$ - 10%

Where π_A and π_C are the closure rate at 6 months in the VenaSeal™ system arm and the ETA or surgical stripping arm.

The parameter assumptions are:

- π_A = 95% in the VenaSeal™ system arm and π_C = 95.4% and 84.8% in ETA and surgical stripping arm, respectively
- Likelihood Score (Farrington & Manning) test with one sided α 0.0167
- 1:1 randomization
- 10% attrition rate.

With these assumptions, a total of 264 subjects (238 evaluable, 119 in each arm) will yield 80% power to reject the null hypothesis in favor of the alternative hypothesis of non-inferiority to the ETA arm. A total of 98 subjects (88 evaluable, 44 in each arm) will yield 80% power to reject the null hypothesis in favor of the alternative hypothesis of non-inferiority to the surgical stripping arm.

Overall Sample Size Evaluation

Power Analysis and Sample Size (PASS) was used to compute sample size. Based on the above fixed sample size calculations, the total sample size in the VenaSeal vs ETA study will be 264 to demonstrate the success on each primary endpoint with at least 90% power **Table 19.**

The total sample size in the VenaSeal vs Surgical Stripping Study will be 108 subjects due to the enrollment closure on 22-Feb-2022.

Table 19: Sample Size for Randomized Studies

Primary or Key Secondary Endpoint	Total Sample Size: VenaSeal and ETA Arms	Total Sample Size: VenaSeal and Surgical Stripping Arms
VenousTSQe at 30 days	237	237
VenousTSQs at 30 days	237	237
Elimination of truncal reflux at index procedure	227	220
Return to work	22	10

Closure rate at 6 months	264	98
Overall Sample Size (Including Attrition)	**264**	**237**

14.1.3. Interim Analysis

No interim analysis for early stopping is planned for the VenaSeal vs. ETA Study or the VenaSeal vs. Surgical Stripping Study.

14.1.4. Analysis Sets

The primary analysis set for Randomized Studies will be the ITT analysis set. Per-protocol (PP) analyses may be performed as a sensitivity analysis. All analysis sets have been defined with the intent of minimizing bias in the data analysis.

Intent-to-Treat (ITT): All patients who are randomized in the arms in each study will be included in the analysis regardless of the treatment received or the outcome of the treatment.

Per-Protocol (PP): The ITT population excluding failed and no procedure treatment outcomes, subjects that are treated with the modality they were not randomized to and/or have not met the inclusion/exclusion criteria.

As treated (AT): Includes subjects in the arm they are treated with according to the treatment actually received, regardless of the arm they were randomized to.

14.2. VLU Study (Single-Arm Study)

Analyses will be performed on all enrolled patients with CEAP 6 as according to the inclusion/exclusion criteria.

Descriptive statistics will be presented for the study endpoints.

14.2.1. Sample Size Consideration

The primary endpoint in the VLU Study is time to ulcer healing. For reference, the EVRA study[38] evaluated clinical and cost effectiveness of early endovenous treatment and standard care vs. deferred intervention in patients with chronic venous ulceration. As there are no statistically powered hypotheses in the VLU Study, precision estimates (distance from point estimate to the max of lower or upper 95% two-sided confidence bound) were used to derive the sample size based on the outcomes of the EVRA study.

In comparison to the EVRA study, criteria for VLU Study inclusion is less restrictive, which may result in an ulcer population which is older and heals more slowly than the EVRA early-intervention group. Precision calculations utilized an assumed median time to healing of 70 days which is the approximate average of the median healing time between the EVRA early-intervention and deferred-intervention groups (56 and 82 days, respectively). Precision estimates for a range of sample sizes are provided in **Table 20**. A simulation is run 10,000 times on the assumption of exponential distribution of 70 days median time to healing. The simulation result shows the precision of less than 23 days can be obtained with a sample size of 125 subjects enrolled into the VLU Study.

Table 20: Sample Size for the VLU Study

Sample size	Evaluable Sample Size (10% attrition)	Precision
80	72	<30 days
90	81	<28 days
100	90	<26 days
110	99	<25 days
115	104	<24 days
120	108	<24 days
125	113	<23 days

14.2.2. Interim Analysis

No interim analysis is planned for this CEAP 6 single arm study.

14.2.3. Analysis Sets

Intention-to-Treat (ITT): All patients with CEAP 6 who are enrolled in this study (either successful, incomplete or failed treatment outcome) will be counted in the ITT population, which will be the primary analysis set.

Per-Protocol (PP): The ITT population excluding failed treatment outcome and/or subjects that have not met the inclusion/exclusion criteria

The primary analysis for this CEAP 6 single arm study will be on intention-to-treat (ITT) population. All analysis sets have been defined with the intent of minimizing bias in the data analysis.

14.3. Analysis of Safety Events

Descriptive statistics for the safety events will be provided. Quantitative variables will be presented with mean and standard deviation or median, minimum and maximum as appropriate. Qualitative variables will be presented with frequency and percentage. The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot. AEs will be tabulated and reported using the current version of MedDRA dictionary. SAEs will be tabulated and reported up to 60 months.

14.4. Analysis of Baseline Characteristics

All clinically relevant baseline variables will be tabulated and reported. Quantitative variables will be presented with mean and standard deviation or median, minimum and maximum as appropriate. Qualitative variables will be presented with frequency and percentage.

14.5. Safety Event Analysis and Reporting of Results

Patient data listings and tabular and graphical presentations of results will be provided if needed.

14.6. Health Economics Analysis

This study will collect healthcare utilization data related to subject's VRD and care related to the VenaSeal™ closure system to demonstrate total costs over the follow-up period.

US cost and global effectiveness data collected in the study will be used to validate and update VenaSeal™ system US cost-effectiveness model developed by Medtronic. The healthcare utilization data from non-US countries will then be transformed to identified regional costs which will then be used as model parameters for global regional cost-effectiveness and/or budget impact model adaptations.

Specific analysis will focus on additional VLU healthcare utilization for all ulcers on the target limb, including routine wound care treatment through ulcer healing. The additional VLU healthcare utilization will not be only limited to routine wound care treatments but also any other unscheduled healthcare utilizations including office visits and emergency room visits.

14.7. Missing Data

Every effort will be undertaken to minimize missing data. Unless otherwise specified, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. The number of patients included in each analysis will be reported so that the reader can assess the potential impact of missing data.

15. Ethics

15.1. Statement(s) of Compliance

The VenaSeal Spectrum study will be conducted in compliance with international ethical and scientific quality standards, known as Good Clinical Practice (GCP). GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study. This study is designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. 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. In accordance with ISO 14155:2020, 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 investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. The process of reporting AE and DD handling in this study is ISO 14155:2020 compliant for all participating geographies.

The study will be conducted according to the Clinical Investigation Plan, CTA, 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 process, IRB/EC/CA approval, study training and clinical study registration, risk-benefit assessment and publication policy.

Ultimately, all study sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The CTA
- The procedures described within this CIP
- Local EC Requirements.

In addition to the regulatory requirements outlined above, 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. These include but are not limited to:

- In the US, the study will be conducted in compliance with 21 CFR Parts 50 (Protection of Human Subjects) and 56 (IRBs).
- In Canada, SOR/98-282, Section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60(1).
- In Europe the study will be conducted in compliance with the MDD 93/42/EEC, EU MDR 2017/745.
- In all geographies except US, the study will be conducted in compliance with ISO 14155:2020, with an exception that this study only collects a subset of adverse events.

The study will be publicly registered prior to in accordance with 42 CFR part 11 and Declaration of Helsinki on http://clinicaltrials.gov. In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent EC or IRB.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the study site.

Due to the post-market nature of this study and because this study does not include a primary safety endpoint, the scope of AE reporting in this study has been limited to reporting of events listed in section 12 and no device accountability is required with exception of documenting a reference to the used device in the CRF (this is a deviation from ISO 14155:2020). The subject enrollment definition for this study is 'the moment of randomization' for CEAP 2-5 subjects and 'the moment the first component of VenaSeal™ system enters the body' for CEAP 6 subjects; this is also a deviation from ISO 141155:2020.

The EUDAMED generated single identification number of the clinical investigation will be provided under a separate cover when available.

16. Study Administration

16.1. Clinical Trial Agreement

Medtronic contracts with participating institutions/investigators through a CTA that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic. A CTA shall be in place, signed by the participating investigational site and/or PI 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 this clinical investigation plan and subsequent amendments, with a fully executed agreement.

16.2. Subject Compensation

Subjects will receive a fixed amount of compensation as applicable/allowed per region for the time spent completing the questionnaires and other documentation, and for transportation to and from the study visits and other related costs that may be incurred for study participation. Medtronic may provide reimbursement for subjects 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.

16.3. Site Activation / Supply of Trial Materials

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

- Clinical Trial agreement
- CA approval (as applicable to the geography)
- Ethic Boards approval
- Medtronic and Ethic Boards approved ICF/Data release form (DRF) document, and other information provided to the subject
- Curriculum vitae of the PI, Sub-Investigators, and all key site staff
- Financial Disclosure from the investigators
- Delegated Task List
- Documented training of the investigative team

- It is expected that product training per standard Medtronic requirements will be completed by all treating physicians prior to his/her enrolling subjects into the study. A treating physician may be included in the clinical study if compliant with the following:
    - Physician is an appropriately qualified practitioner legally authorized to practice in his/her respective region, and experienced in the diagnosis and endovascular treatment of patients requiring superficial truncal vein treatment.
    - Physician has demonstrated experience with conducting clinical trials that comply with applicable regulatory standards.

16.4. Monitoring

Monitoring and monitoring oversight will be provided by Medtronic and detailed in a Monitoring Plan separate from this CIP.

A site qualification visit may be conducted by Medtronic personnel (or designees) in person or remotely to review the clinical investigational plan and, regulatory and study requirements with the investigator and study personnel.

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. These visits may be in person or remotely, as allowable per local site regulations.

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with the Monitoring Plan, either in person or remotely, as allowable per local site regulations.

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 CTA, this Investigational Plan, the applicable laws and regulations, or the requirements of the reviewing IRB/EC/CA, prompt action will be taken to secure compliance. Medtronic will reserve the right to suspend or terminate the participation of the investigator or the investigational site.

During the routine monitoring visit, it may be verified whether signed and dated ICF/DRF forms have been obtained from each subject before any clinical study related procedures are undertaken. Medtronic or designee will conduct site monitoring visits to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

A risk-based monitoring plan will be followed, this is outlined in further detail within the Monitoring Plan. 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, either on-site or remotely, as per regulatory requirements:

- Direct access to the electronic source document(s) with Monitor's login details and limited access to study subjects.
- Direct access to the electronic medical record(s), or direct access to the electronic medical record(s) by reviewing alongside appropriate study staff.
- Copies of the electronic medical record signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

16.5. Data Management

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained by Medtronic in accordance with applicable regulations.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets and subject medical records must be created and maintained by the investigational study site team.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. See section 10.15 for CRFs and data collection elements that may be considered source.

It is recommended to complete CRFs no later than 10 working days after each procedure or follow-up visit, except for CRFs documenting AEs or device deficiencies that require immediate reporting (refer to **Table 14** for the reporting requirements). Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this study. The study database will employ validation programs (e.g., range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation.

16.6. Direct Access to Source Data/Documents

The PI and the study team shall be accessible to Medtronic representative, monitoring team and the clinical study manager. This accessibility is of particular importance for reviewing data in the CRF.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents or be approached to upload source documents into a secure system, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, IRB/EC review, and regulatory inspections.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform Medtronic and authorize Medtronic to participate in this inspection.

16.7. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Each enrolled subject will be assigned to a unique subject ID number (SID), which is pre-configured in Electronic Data Capture (EDC) system. Records of the subject/SID relationship will be maintained by the study site. The SID is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any study document other than the subject's ICF. In the event a subject's name is included for any reason, it will be immediately 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 RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. 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 general, Sponsor's representatives, IRB/EC and CA members, European or other international public regulatory authorities may have access to subject confidential information.

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 ICF. 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.

16.8. Liability

The sponsor and local sponsors are wholly owned subsidiaries of Medtronic. Medtronic (including all wholly owned subsidiaries companies) maintains appropriate clinical study 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 Study Insurance statement or certificate will be provided to the EC/IRB and CA, if applicable.

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

16.9. CIP Amendments

The investigator will propose any appropriate modification(s) of the clinical investigation plan or product use when needed. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the clinical investigation plan, including a justification for this amendment, to the appropriate regulatory authorities, IRBs/ECs and to the investigators. The investigator will only implement the amendment after approval of the IRB/EC, regulatory authority (if applicable) and sponsor. Furthermore, investigators shall sign any approved amendment for agreement.

16.10. Record Retention

All study-related documents must be retained for a period of at least 2 years after study closure or longer if required by local law. Medtronic will inform the investigator/study 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 per local regulations.

16.10.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years or longer as required by local law:

- All correspondence between the IRB/EC/CA, sponsor, monitor, regulatory authority and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated ICF.
    - Observations of AEs/ADEs/DDs.
    - Medical history.
    - Procedure and follow-up data (if applicable).
    - Documentation of the dates and rationale for any deviation from the protocol.
- Randomization list (for the Randomized Studies).
- List of investigation study sites.
- Financial Disclosure as applicable.
- Subject Pre-screening log and Subject Identification & Enrollment log.
- All approved versions of the CIP, ICF.
- Signed and dated CTA.
- CV of PI and key members of investigation study site team (as required by applicable regulations.
- Documentation of delegated tasks.
- Regulatory Approval notification, correspondence and approval, where required per local law.

- Study training records for study site staff.
- Insurance certificates as applicable.
- Final Study Report including the statistical analysis.

16.10.2. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation.
- Signed Investigator Trial Agreements, Financial Disclosure and current signed and dated CV of PI and key members of the investigation study site team (as required by local law), delegated task list.
- All approved ICF templates, and other information provided to the subjects and advertisements, including translations.
- Randomization records (for the Randomized Studies).
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance.
- Names of the institutions in which the study will be conducted.
- RA correspondence, notification and approval as required by national legislation.
- Insurance certificates as applicable.
- Names/contact addresses of monitors.
- Monitoring visit reports.
- Statistical analyses and underlying supporting data.
- Final report of the study.
- The CIP, and study related reports, and revisions.
- Study training records for study site personnel and Medtronic personnel involved in the study.
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system. After closure of the study Medtronic will archive records and reports per local regulations.

16.11. Reporting Requirements

16.11.1. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects, device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by IRB/EC/CA with respect to this

study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in section 12. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 21: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC/CA approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given in a timely manner after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs/ECs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

Table 22 : Investigator reports applicable to Europe and Middle East per ISO 14155

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	Report if required by local law.
Progress Report	Sponsor and IRB/EC	Provide if required by local law or IRB/EC.
Study Deviations	Sponsor, CA and IRB/EC	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees, CAs or the appropriate RAs should be informed. (ISO 14155:2020)
Failure to obtain IC	Sponsor and IRBs/ECs	IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2020)

16.11.2. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of the reviewing IRB/EC, RA or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in section 12.

Table 23: Sponsor reports for Australia

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, and relevant authorities	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020).
Recall and device disposition	Investigators, Head of Institution, IRB/EC, and relevant authorities	Notification as per the local requirements in Australia.

Report	Submit to	Description/Constraints
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

Table 24: Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Head of Institution, IRB/EC, relevant authorities	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Study site specific study deviations will be submitted to investigators periodically.

Table 25: Sponsor reports for Europe and Middle East

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)
Withdrawal of IRB/EC approval	Investigators, Head of Institution, IRB/EC and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Withdrawal of CA approval	Investigators, Head of Institution, IRB/EC, and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Progress Reports	IRB/EC and RAs	This will be submitted to the IRB/EC only if required by the IRB//EC).
Final report	Investigators, IRB/EC, and RAs if required	For studies with study sites complying to ISO 14155: • 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 coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the PI in each study site should be obtained. (ISO 14155:2020)

Report	Submit to	Description/Constraints
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

16.12. Publication and Use of Information

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. Publications from this study will be handled according to Standard Operating Procedures and as indicated in the CTA.
The following publication policy will apply to all participating investigational sites:

- Medtronic may use the study data for regulatory authority submission, may publish the results in peer reviewed scientific journal(s) and present the data at major congresses.
- Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.
- The number of authors will be dependent on the regulations of the concerning journal. Names of all participating investigators will appear in the Acknowledgment of the paper, if allowed by the journal.
- Based on the principle that Medtronic owns the data of this clinical study, a single investigational site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.
- Pooling data from several investigational sites for publication purposes, national projects and international projects all require prior approval from Medtronic.
- Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified. Participating subjects will not be identified by name in any published reports about the clinical study.

16.13. Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRB, ECs and CAs of participating countries when required by local law.
- Registering and posting the study results on a publicly accessible database, e.g., ClinicalTrials.gov based on the posting rules stipulated.
- Submitting for publication the primary study results when available.
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences.
- Making an individual study site study data accessible to the corresponding investigator after the completion of the study, if requested.

16.14. Suspension or Early Termination

Early study suspension or termination

Medtronic reserves the right to complete the study earlier (i.e., longer-term follow-up visits may not be completed). Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site. Medtronic also reserves the right to suspend or terminate the study for any other reason than the ones listed above.

Early investigational site suspension or termination

Medtronic, IRB/EC or regulatory authority may decide to suspend or prematurely terminate an investigational site. If an investigational site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/EC and the study subjects.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigational site and immediately inform the sponsor and IRB/EC, if applicable.

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 IRB/EC/CA 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.).
- IRB/EC/CA 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).

Subject follow-up in case of termination

In case of early termination, all subjects should be followed by their physicians per standard care and no further patient data will be collected under this clinical investigation plan.

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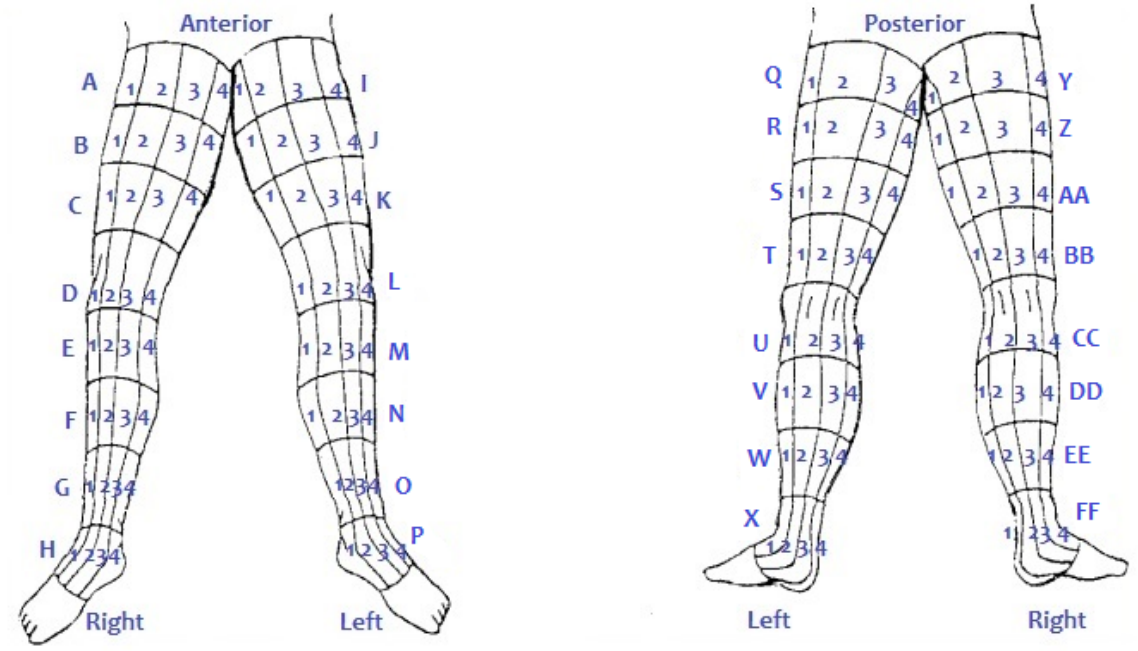
18. Appendices

Appendix A: Patient Questionnaires and Assessments

1. AVVQ

1. Were your varicose veins present in 1 or more segments? If yes, please specify the segments



Check off segments below that were shaded by patient

☐ No segments were shaded by patient

ANTERIOR								POSTERIOR							
Right					Left			Left					Right		
A	☐1	☐2	☐3	☐4	I	☐1	☐2	☐3	☐4	Q	☐1	☐2	☐3	☐4	Y	☐1	☐2	☐3	☐4
B	☐1	☐2	☐3	☐4	J	☐1	☐2	☐3	☐4	R	☐1	☐2	☐3	☐4	Z	☐1	☐2	☐3	☐4
C	☐1	☐2	☐3	☐4	K	☐1	☐2	☐3	☐4	S	☐1	☐2	☐3	☐4	AA	☐1	☐2	☐3	☐4
D	☐1	☐2	☐3	☐4	L	☐1	☐2	☐3	☐4	T	☐1	☐2	☐3	☐4	BB	☐1	☐2	☐3	☐4
E	☐1	☐2	☐3	☐4	M	☐1	☐2	☐3	☐4	U	☐1	☐2	☐3	☐4	CC	☐1	☐2	☐3	☐4
F	☐1	☐2	☐3	☐4	N	☐1	☐2	☐3	☐4	V	☐1	☐2	☐3	☐4	DD	☐1	☐2	☐3	☐4
G	☐1	☐2	☐3	☐4	O	☐1	☐2	☐3	☐4	W	☐1	☐2	☐3	☐4	EE	☐1	☐2	☐3	☐4

H ☐1 ☐2 ☐3 ☐4	P ☐1 ☐2 ☐3 ☐4	X ☐1 ☐2 ☐3 ☐4	FF ☐1 ☐2 ☐3 ☐4

2. In the last two weeks for how many days did your veins cause you pain or ache?

	Right Leg	Left Leg
None at all	O	O
Between 1 and 5 days	O	O
Between 6 and 10 days	O	O
For more than 10 days	O	O

3. During the last two weeks, how many days did you take painkilling tablets for your varicose veins?

	Right Leg	Left Leg
None at all	O	O
Between 1 and 5 days	O	O
Between 6 and 10 days	O	O
For more than 10 days	O	O

4. In the last two weeks, how much ankle swelling have you had?

O None at all
O Between 1 and 5 days
O Between 6 and 10 days
O For more than 10 days

5. In the last two weeks, have you worn support stockings or tights?

	Right Leg	Left Leg
No	O	O
Yes, those I bought myself without prescription	O	O
Yes, those prescribed by my doctor which I wear occasionally	O	O
Yes, those prescribed by my doctor which I wear every day	O	O

6. In the last two weeks, have you had any itching in association with your varicose veins?

	Right Leg	Left Leg

No	O	O
Yes, above the knee only	O	O
Yes, below the knee only	O	O
Yes, above and below the knee	O	O

7. Do you have purple discoloration caused by tine blood vessels in the skin, in association with your varicose veins?

	Right Leg	Left Leg
No	O	O
Yes	O	O

8. Do you have a rash or eczema in the area of your ankle?

	Right Leg	Left Leg
No	O	O
Yes, but it does not require treatment from a doctor or district nurse	O	O
Yes, and it requires treatment from a doctor or district nurse	O	O

9. Do you have a skin ulcer associated with your varicose veins?

	Right Leg	Left Leg
No	O	O
Yes	O	O

10. Does the appearance of your varicose veins cause you concern?

O None at all
O Yes, their appearance causes me slight concern
O Yes, their appearance causes me moderate concern
O Yes, their appearance causes me a great deal of concern

11. Does the appearance of your varicose veins influence your choice of clothing including tights?

O No
O Occasionally
O Often
O Always

12. During the last two weeks, have your varicose veins interfered with your work/housework or other activities?

O No
O I have been able to work but my work has suffered to a slight extent
O I have been able to work but my work has suffered to a moderate extent
O My veins have prevented me working one day or more

13. During the last two weeks, have your varicose veins interfered with your leisure activities? (Including sports, hobbies, and social life)

O No
O Yes, my enjoyment has suffered to a slight extent
O Yes, my enjoyment has suffered to a moderate extent
O Yes, my veins have prevented me taking part in any leisure activities

2. EQ-5D-5L

Health Questionnaire

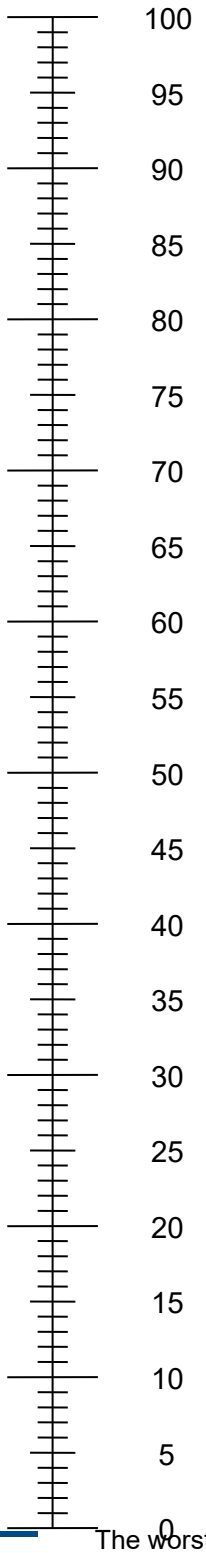
English version for the USA

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	❑

The best health you can imagine

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 = ☐



The worst health you can imagine

3. rVCSS

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 or other discomfort (i.e. aching, heaviness, fatigue, soreness, burning) 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 "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position		Few: scattered (i.e., isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous Edema Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin Pigmentation Presumes venous origin 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 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 Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis, hypodermitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

Includes white atrophy and ipodermatosclerosis				
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 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

4. SF-36

Patient Name: _____

1. In general, would you say your health is:
(Circle One Number)

Excellent 1
Very Good 2
Good 3
Fair 4
Poor 5

2. **Compared to one year ago**, how would you rate your: general health right **now** ?
(Circle One Number)

Much better than one year ago 1
Somewhat better than one year ago 2
About the same 3
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

The following items are about activities you might do during a typical day: Does **your health now limit you** in these activities? If so, how much? **(Circle One Number on Each Line)**	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. **Moderate activities**, such as moving a table pushing a vacuum cleaner, bowling or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing **several** fights of stairs	1	2	3
7. Climbing **one** flight of stairs	1	2	3
8. Bending, kneeling or stooping	1	2	3
9. Walking **more than a mile**	1	2	3
10. Walking **several blocks**	1	2	3
11. Walking **one block**	1	2	3
12. Bathing or dressing yourself	1	2	3

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 physical health** ?: **(Circle One Number on Each Line)**	Yes	No
13. Cut down the amount of time you spend on work or other activities	1	2
14. Accomplish less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, took extra effort)	1	2

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 any emotional problems** ?: (depressed, anxious) **(Circle One Number on Each Line)**	Yes	No
17. Cut down the amount of time you spend on work or other activities	1	2
18. Accomplish less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?
(Circle One Number)

Not at all 1
Slightly 2
Moderate 3
Quite a bit 4
Good 5

21. How much **bodily** pain have you had during the **past 4 weeks**:
(Circle One Number)

None 1
Very Mild 2
Mild 3
Moderate 4
Severe 5
Very Severe 6

22. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework ?
(Circle One Number)

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

These questions are about how you feel and how things have been with you **during the past 4 weeks**. 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 . . . **(Circle One Number 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
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up ?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Do you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, to what extent has your **physical health or emotional problems** interfered with your normal social activities like visiting with family, friends, relatives, etc.?
(Circle One Number)

All of the time 1
Most of the time 2
Some of the time 3
A little of the time 4
None of the time 5

How TRUE or FALSE is each of the following statements for you?

(Circle One Number on Each Line)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Comments: _____

_____

Patient Signature: _____ Date _____

5. CEAP Classification

The CEAP classification 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 per 2004 guidelines

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

CLINICAL CLASSIFICATION per 2020 guidelines

C0: no visible or palpable signs of venous disease
C1: telangiectasies or reticular veins
C2: varicose veins
    C2r: recurrent varicose veins
C3: edema
C4a: pigmentation and eczema
C4b: lipodermatosclerosis and atrophie blanche
C4c: corona phlebectatica
C5: healed venous ulcer
C6: active venous ulcer
    C6r: recurrent active venous ulcer

6. VenousTSQ

Both components of the VenousTSQ, the peri-procedural early component of the venous treatment satisfaction (VenousTSQe) and the status component of the venous treatment satisfaction questionnaire (VenousTSQs) are provided below.

Venous Treatment Satisfaction Questionnaire – early

(VenousTSQe)

You have recently had a procedure to treat varicose veins. The following questions are concerned with your experience before, during and / or after the procedure. Please answer each question by circling a number on the scale and / or checking a box.

1a. Before the procedure, were you given any information about the following possible aspects of treatment for your varicose veins? Please check one box for each aspect of treatment below.

		yes	no	don't recall
i.	Details of planned procedure	☐	☐	☐
ii.	Expected levels of discomfort / pain involved with the procedure	☐	☐	☐
iii.	Side effects / after-effects	☐	☐	☐
iv.	Recommended or restricted activities / movements	☐	☐	☐
v.	Post-procedure care (including self-care)	☐	☐	☐
vi.	Recovery time	☐	☐	☐

1b. Before the procedure, were you given any of the above information in written form?

yes ☐ no ☐ don't recall ☐

1c. Overall, how satisfied are you with the information you were given?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

2. How apprehensive did you feel before the procedure to treat your varicose veins?

not at all apprehensive 6 5 4 3 2 1 0 very apprehensive

3. How bothered were you by the amount of discomfort or pain you had during the procedure?

not at all bothered 6 5 4 3 2 1 0 very bothered

continued on the next page …

VenousTSQe continued …

4. How unpleasant did you find the procedure?

not at all unpleasant 6 5 4 3 2 1 0 very unpleasant

5a. Immediately after the procedure, did you wear compression stockings or bandages?

no ☐ If *no*, please go straight to Q. 6a.

yes ☐ If *yes*, please answer Q. 5b below.

5b. How bothered were you by wearing compression stockings / bandages?

not at all bothered 6 5 4 3 2 1 0 very bothered

6a. Were there any restrictions on bathing after the procedure?

no ☐ If *no*, please go straight to Q.7.

yes ☐ If *yes*, please answer Q. 6b below.

6b. How bothered were you by restrictions on bathing?

not at all bothered 6 5 4 3 2 1 0 very bothered

7. Overall, how easy or difficult did you find your treatment?

very easy 6 5 4 3 2 1 0 very difficult

8a. Has there been any cost to you associated with your treatment?

no ☐ If *no*, please check the box.

yes ☐ If *yes*, please answer Q. 8b below.

8b. How satisfied are you with any cost to you associated with your treatment?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

If you have any comments you would like to make about your experience before, during and / or after the procedure, please use the box below.

Thank you. Please go to the next page.

Venous Treatment Satisfaction Questionnaire – status

(VenousTSQs)

The following questions are concerned with your experience since treatment for your varicose veins. Now we would like to know about your experience in recent weeks, including any:

- **medication**
- **compression stockings or bandages**
- **exercise**
- **treatment of venous ulcers**

Please answer each question by circling a number on the scale and / or checking a box.

1. How satisfied are you with your treatment for vein problems?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

2. How well do you feel your vein problems are controlled now?

very well controlled 6 5 4 3 2 1 0 very badly controlled

3a. In recent weeks, have you experienced any discomfort or pain related to your treatment?

no ☐ If *no*, please go straight to Q. 4a.

yes ☐ If *yes*, please answer Q. 3b below.

3b. How bothered are you by the discomfort or pain?

not at all bothered 6 5 4 3 2 1 0 very bothered

4a. In recent weeks, have you experienced any side effects or after-effects of your treatment?

no ☐ If *no*, please go straight to Q. 5a.

yes ☐ If *yes*, please answer Q. 4b below.

4b. How bothered are you by the side effects or after-effects?

not at all bothered 6 5 4 3 2 1 0 very bothered

5a. In recent weeks, have you worn compression stockings or bandages?

no ☐ If *no*, please go straight to Q. 6.

yes ☐ If *yes*, please answer Q. 5b below.

5b. How bothered have you been by wearing compression stockings / bandages?

not at all bothered 6 5 4 3 2 1 0 very bothered

continued on the next page …

VenousTSQs continued …

6. How satisfied are you with your understanding of your vein problems?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

7a. Have you returned to all your usual activities since your varicose vein procedure?

yes ☐ no ☐

Whether you answered *yes* or *no*, please answer Q. 7b.

7b. How satisfied are you with the time taken to return to your usual activities?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

8. How satisfied have you been in recent weeks with the effects of the treatment on your independence?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

9. Would you recommend your treatment to someone else who is being offered this vein treatment?

yes, I would definitely recommend the treatment 6 5 4 3 2 1 0 no, I would definitely not recommend the treatment

10. If you needed further vein treatment, how satisfied would you be to have the same treatment?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

11. Are there any other aspects of the treatment for vein problems, causing either satisfaction or dissatisfaction, which have not been covered?

yes ☐ no ☐

If **yes**, please describe below.

Thank you for taking the time to complete this questionnaire.

VenousTSQs © Prof. Clare Bradley 8.8.19 English for USA 19.11.19 (from Std UK English rev. 19.11.19) Page **4** of **4**
Health Psychology Research Unit, Royal Holloway, University of London, Egham, TW20 0EX, UK.

7. VenousDQoL Overview items

VenousDQoL Overview Items

These questions ask about your quality of life – in other words how good or bad you feel your life is.

Please put an "X" in the box that best indicates your response for each item.

What we would like to know is how you feel about your life now.

I) In general, my present quality of life is:

☐ excellent	☐ very good	☐ good	☐ neither good nor bad	☐ bad	☐ very bad	☐ extremely bad

Now we would like to know how your quality of life is affected by your varicose veins, their treatment and any side effects and/or complications you may have.

II) If I did *not* have varicose veins, my quality of life would be:

☐ very much better	☐ much better	☐ a little better	☐ the same	☐ worse

8. Patient Reported Symptoms Table

ACHING	o NO o YES	☐ DOMINANT SYMPTOM
BURNING	o NO o YES	☐ DOMINANT SYMPTOM
HEAVINESS	o NO o YES	☐ DOMINANT SYMPTOM
ITCHING	o NO o YES	☐ DOMINANT SYMPTOM
PAIN	o NO o YES	☐ DOMINANT SYMPTOM
SENSITIVITY	o NO o YES	☐ DOMINANT SYMPTOM
SWELLING	o NO o YES	☐ DOMINANT SYMPTOM

9. Patient Prior History Table

Superficial and deep venous treatment history

Medical History Term	Prior History	Limb	Level of Satisfaction with Treatment	How many years ago?
Thermal ablation (laser, RF)	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
Non-thermal ablation (MOCA, PEM)	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
CAC	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
Ultrasound-guided foam sclerotherapy	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
Stripping	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years

Cosmetic sclerotherapy	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
Ambulatory phlebectomy	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
Deep venous stent	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years
Other (specify)	o NO o YES	o Right o Left	o Very dissatisfied o Somewhat dissatisfied o Somewhat satisfied o Very satisfied	o Last year o 1-2 years o 3+ years

Appendix B: Definitions

Term	Definition
Aborted Treatment	Failed completion of the assigned treatment where the subject was prepped for the index procedure, but the device did not enter the vasculature or surgical stripping was not initiated.
Acute superficial thrombophlebitis	Thrombus induced inflammation of a vein in a time period <14 days from symptom onset. It presents with skin redness and tenderness around the hardened vein due to the associated inflammation. It is also commonly referred as superficial vein thrombosis.
Adjunctive treatment	Secondary treatment (phlebectomy and/or sclerotherapy) used to treat remaining varicosities after index procedure for cosmesis, to lessen the risk of superficial thrombophlebitis or because it may enhance primary treatment effectiveness.
As Treated (Analysis set for CEAP 2-5 subjects)	Includes subjects in the arm they are treated with according to the treatment actually received, regardless of the arm they are randomized to.
Circumferential ulcer	An ulcer that extends around the circumference of the leg and out of sight and, or an ulcer that cannot be captured in a single photograph with equipment provided by ulcer core laboratory.
COVID-19	Corona Virus Disease 2019, a new contagious disease caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2).
Endothermal Ablation Treatment (ETA)	Radiofrequency or laser ablation treatment available per site standard practice for the treatment of superficial venous reflux.
Granuloma	A grouping of macrophages. Non-specific.
Hypersensitivity reaction	An allergic reaction to a foreign body/substance.
Incomplete Treatment	The index procedure was commenced where the device entered the vasculature, or the surgical stripping procedure was initiated but for any reason full target vein length was not treated.

Intent to Treat (ITT) (Randomized studies; CEAP 2-5 subjects)	All patients who are randomized in the study will be included in the randomized arm in the analysis regardless of the treatment received.
Intent to Treat (ITT) (VLU Study; CEAP 6 subjects)	All patients with CEAP 6 who are enrolled in this study and successfully treated with VenaSeal™ system, will be counted in the ITT population.
No Procedure treatment outcome (CEAP 2-5)	Subject is randomized (considered enrolled) but withdraws from the study after randomization without any attempt to conduct the procedure (e.g. COVID-19 exclusion, subject withdrawal, etc.).
Per-Protocol (PP) (CEAP 2-6)	The ITT population excluding subjects that are not treated with the assigned treatment modality and/or have not met the inclusion/exclusion criteria.
Phlebectomy	Surgical procedure to remove small varicose veins through a series of small (1-3 cm) incisions in the leg along the GSV and its tributaries.
Phlebitis	Inflammation of a vein, the grading of the phlebitis are as follows and subject may have more than one grading: P1: Inflammation of truncal or epifascial vein post-treatment, with palpable and/or non-palpable (Superficial thrombophlebitis) areas. Located within the treatment zone. It is caused due to Damage to treated vein by prescribed treatment with and without thrombus. P2: Superficial thrombophlebitis in residual varicosities/tributaries. Located outside of treatment zone. It is caused due to thrombosis of draining varices or tributaries secondary to closure of truncal vein P3: Inflammation of cutaneous and subcutaneous tissue. Located within or outside of treatment zone and adjacent tissues. It is caused due to tissue reaction to treatment or hypersensitivity.
Point of Enrollment (CEAP 2-5)	Subjects will be considered enrolled from the moment of randomization.
Point of Enrollment (CEAP 6)	Subjects will be considered enrolled from the moment the first component of the VenaSeal™ delivery system enters the body.

Pre-Screen Failure	Patients that were identified for screening (consenting in the study) but were not consented in the study
Pre-Screening	The process of identifying patients for potential inclusion in the study, prior to obtaining informed consent from the patient.
Primary Target Vein	The primary target vein should be the saphenous vein (GSV, SSV, accessory saphenous veins) which at the investigator's discretion is most likely responsible for the greatest portion of the patient's symptoms or pathology. This vein will be treated first.
Reintervention	Retreatment of any segment of the target vein in the target limb previously treated as part of the study at the index procedure.
Sclerotherapy	Non-surgical procedure where an irritant (i.e. sclerosant) is directly injected into the vein, leading to irreversible endothelial injury and causing the vein to spasm and collapse.
Screen Failure	Subjects who signed and dated the Informed Consent Form, but who no longer meet all eligibility criteria before the point of enrollment.
Screened	Subjects who meet all eligibility criteria will be considered screened from the moment they have signed and dated the ICF
Successful treatment	Completion of the assigned treatment including any reattempt to complete the index procedure.
Target limb	Target limb is the limb identified to be treated limb in the study. In case of bilateral disease with both limbs meeting study eligibility criteria, the treating physician designating the more severe limb depending on the higher CEAP score or most symptomatic according to the patient will be the target limb.
Target Vein (s)	Any additional superficial truncal vein (s) in the target limb beyond the primary target vein which will be treated after the PTV during the index procedure.
Treatment zone	Broad and linear area surrounding the target vein and access site.

Thrombophlebitis migrans	Advancing or migratory thrombophlebitis that involves multiple vessels at the same time.
Thrombus extension: a. Endothermal Heat Induced Thrombus extension (EHIT) b. Endothermal Glue Induced Extension (EGIT)	Extensions of a thrombus that extend from the treated vein (GSV, SSV, ASV) into the deep venous system. Three different types of extension with VenaSeal to be distinguished: 1. A pure glue extension – this looks like a very thin line and is rigid, and is detected immediately after the procedure. 2. A glue/thrombus combination: This glue/thrombus combination is detected immediately after the procedure like pure glue extension. 3. Thrombus extensions: This could be detected at all intervals/follow up periods after the procedure.
Ulcer healing rate	Percent of the ulcer area healed and calculated per given time period on the target limb. The percent healed is determined by an independent core laboratory.
Ulcer recurrence	First occurrence of ulcer re-appearance after it has healed.
Ulcer-free time	Calculated as time between ulcer healing and first instance of ulcer recurrence.
VenaSeal vs. ETA Study	One of the two Randomized Studies in the protocol comparing the VenaSeal™ closure system to endothermal treatment modality
VenaSeal vs. Surgical Stripping Study	One of the two Randomized Studies in the protocol comparing the VenaSeal™ closure system to surgical stripping treatment modality
Venous leg ulcer (VLU) site	The site that is invited to enroll CEAP 6 subjects. This will be indicated in the Site Selection Letter.
VLU Study	Single-arm venous leg ulcer study within the protocol; no comparator

19. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
1.0	Not applicable, New document	NA to this version of the template	NA to this version of the template	NA to this version of the template	Stephanie Geerts-Hulshof/Sr. Clinical Research Specialist Sara Ortiz/ Sr. Clinical Research Specialist
2.0	Extensive revisions changing the study design from a single-arm study to 3 separate studies: 1. Randomized Studies • VenaSeal vs. ETA Study • VenaSeal vs. Surgical Stripping Study	NA to this version of the template	NA to this version of the template	NA to this version of the template	Sara Ortiz/Sr. Clinical Research Specialist Shital Patel/Clinical Research Specialist

	2. VLU Study Language updated throughout document to indicate differences and similarities between the 3 studies. A redline version of this document is available upon request. Specific updates by section: 1. Investigator Statement: No changes. 2. Glossary: Updates based on language in current version. 3. Synopsis: Updates to reflect changes in subsequent sections. 4. Introduction: Addition of comparator therapy information. 5. Objectives and Endpoints: Updates based on changed study design 6. Study Design: Updates to reflect changes in study design, total expected enrollment numbers, total expected site number, follow-up visit schedule and rationale. 7. Product Description: Updates reflects reference to comparator product's IFU for product description				Awaz Ali/ Clinical Research Specialist

	and site's standard practice for surgical stripping procedure. 8. Selection of Subjects: Updates reflects changes in subject identification and screening process along with updates related to target vein/target ulcer selection. Inclusion and Exclusion criteria are updated based on revised study design. 9. Study Procedures: Updates reflect changes related schedule of events, study assessments, screening, baseline, index procedure and follow-up visits. Randomization details added. 10. Risks and Benefits: Updates reflects reference to comparator product's IFU for risk details and risk-benefit rationale updated based on revised study design. 11. Adverse Events and Device Deficiencies: Recording and reporting of adverse events and device deficiencies (device deficiency reporting only for VenaSeal™ system) updated. 12. Data Review Committees: Updates to include CEC and ulcer core laboratory details. 13. Statistical Design and Methods: Updates based on revised study design related to sample size evaluation and data analysis.				

	14. Ethics: Updates to include study registration on clinicaltrials.gov, EUDAMED identifier, and deviations from ISO 14155:2011. 15. Study Administration: Updates to include language related to randomized and single arm study design and subject compensation details. 16. References: Updates to include references as they are used throughout the document.				
3.0	Specific Updates by Section: 1. Investigator Statement: No changes. 2. Glossary: Updates based on language in current version. 3. Synopsis: Updates to reflect changes in subsequent sections. 4. Introduction: Reference update for CEAP assessment. 5. Objectives and Endpoints: Error related to healthcare utilization data for VLU study corrected to accurately reflect 6 months prior to the index procedure data will not be collected. VenousDQoL added under patient experience secondary endpoints. 6. Study Design: Language updated to clarify the rationale for non-blinded study. The maximum	• Changes to reflect ISO 14155:2020 updates and Version B CIP template in applicable sections. • Changes to clarify study procedures, treatment groups, and timing of data capture. • Changes to accommodate potential impact of COVID 19.	• No potential impact on the performance, effectiveness, or safety. • One additional secondary endpoint added.	• Informed Consent Form • Case Report Forms	Sara Ortiz/Pr. Clinical Research Specialist Shital Patel/Clinical Research Specialist Awaz Ali/Clinical Research Specialist

	enrollment allowed per site updated to accurately reflect maximum allowed per study per site. 7. Product Description: Updates reflects new CIP template requirements. 8. Study Site Requirements: New section added per new CIP template requirement and to reflect ISO 14155:2020 updates. 9. Selection of Subjects: Updates reflects changes in patient follow-up for different treatment outcome category. Allowing usage old ulcer photograph for etiology confirmation added for VLU study. Exclusion criteria updated to add COVID-19 specific exclusion. 10. Study Procedures: Updates reflect changes related to new CIP template and ISO 14155:2020 updates. Added requirement for collecting 2020 CEAP assessment along with 2004 CEAP assessment. Adjunctive therapies and treatment allowed for VLU study modified. 11. Risks and Benefits: Updates reflects changes related to new CIP template and ISO 14155:2020 updates. The potential AE list for VenaSeal™ system modified to reflect the updated VenaSeal IFU. 12. Adverse Events and Device Deficiencies: Updates reflect changes in the Adverse event and device	• New release of CEAP 2020 and VenousDQoL. • Administrative changes.			

	deficiency definitions per ISO 14155:2020 updates along with updates in expected and unavoidable adverse events. Recording and reporting of adverse events and device deficiencies (device deficiency reporting only for VenaSeal™ system and Medtronic ClosureFast™ system) updated. 13. Data Review Committees: Administrative changes to update CEC address. 14. Statistical Design and Methods: Updates related to VenousTSQ language and analysis set definitions clarified. 15. Ethics: Updates reflects changes related to new CIP template and ISO 14155:2020 updates. 16. Study Administration: Updates reflects changes related to new CIP template				
4.0	Updates by section: 1. Cover Page: OU for Sponsor Medtronic Bakken Research Center B. V. deleted, added sponsor Medtronic Canada 2. Document version and date updated throughout the document 3. Section 1: section updated to reflect current internal CIP template	• Per CIP 4.0, the decision of closure of the VenaSeal vs. Surgical Stripping Study enrollment was made due to significant delays and	• No potential impact on the performance, effectiveness, or safety endpoints for the VenaSeal vs ETA study.	• Informed Consent Form • Case Report Forms	Shital Patel, Sr. Clinical Research Specialist Mariapaola Loda, Sr. Clinical Research Specialist

	4. Section 2 (Glossary): added SAP, UADE, USADE, updated VCSS with phrase "revised" 5. Section 3 (Synopsis): OU for Sponsor Medtronic Bakken Research Center B. V. deleted, added sponsor Medtronic Canada. Updated indication codes for US and OUS. Updated details for enrollments in section Study Design. Updated Primary Objective section for VLU. Updated Primary Endpoint section for VLU. Updated secondary endpoints section for Surgical Stripping Study. Updated sample size. Updated exclusion criteria #12. Updated Table 1 (Schedule of Assessments – All Subjects) and added a new footnote related to the follow-up for Surgical Stripping Study. Updated Table 2 (Additional Schedule of Assessments – VLU Study) and added the term "active" to "Target Active Ulcer Assessment". Updated statistics section and specified that primary endpoint for VLU study will be measured through 12 months and added a paragraph about surgical stripping study. 6. Section 4.2 (Purpose): Updated number of subjects that will be enrolled as well as the follow-up for all studies. 7. Section 5.1.1 (Primary Objective): specified that primary objective for VLU study is measured through 12 months.	challenges recruiting sites and patients during the global COVID-19 pandemic. The subjects enrolled in VenaSeal vs. Surgical Stripping Study will still be followed through the 12 month follow-up visit to ensure follow-up through the first year following procedure. • The primary endpoint for the VLU study for time to ulcer healing is updated from	• Primary endpoint for VLU study changed to 12 months from 24 months. • The performance, effectiveness, and safety objectives with follow-up greater than 1 year were reduced to 12 months follow-up in the VenaSeal vs. Surgical Stripping Study.		

	8. Section 5.2.1 (Primary Endpoints): updated primary endpoint for VLU study from 24 to 12 months. 9. Section 5.2.3 (Secondary Endpoints): updated all secondary endpoints for the Surgical Stripping Study through 12 months. 10. Section 6 (Study Design): updates related to the closure of Surgical Stripping Study, follow-up through 12 months for Surgical Stripping Study, number of patients enrolled in the study, maximum number of subjects to be enrolled by each site for VLU study, SAEs have been added to the events that require CEC adjudication. 11. Section 6.1 (Duration): updated enrollment and study duration. Updated duration and collection of data for Surgical Stripping Study. 12. Section 6.2 (Rationale): updated to reflect changes for Surgical Stripping and VLU study. 13. Section 7.1 (Product Description, General): added new VenaSeal system model numbers. 14. Section 7.4 (Product Description, Intended Population): updated VenaSeal system numbers for US and OUS.	24 months to 12 months to align with landmark clinical trials in superficial venous space. • The hypothesis test for the primary endpoint of elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure in VenaSeal vs. Surgical Stripping Study is removed as the endpoint is no longer powered with the reduced sample size. However, results will still be summarized			

	15. Section 8.1 (Investigator/Investigation Site Selection): updated language related to treating physicians. 16. Section 9.1 (Study Population): added language on closure of enrollment for Surgical Stripping Study. 17. Section 9.6 (Exclusion Criteria): updated exclusion criteria #12 on COVID-19. 18. Section 10.1 (Schedule of events and data collection): Updated Table 6 (Schedule of Assessments – All Subjects) and added a new footnote related to the follow-up for Surgical Stripping Study. Data collection language has been updated according to the changes made to the tables. Updated language on standard of care procedures. 19. Section 10.2 (Scheduled Follow-up visit windows): title of table 8 updated for Surgical Stripping Study. Word "implant" changed into procedure. 20. Section 10.3 (Subject Consent): deleted reference to consent templates. 21. Section 10.4 (Randomization and treatment assignment (CEAP 2-5)): updated language on Surgical Stripping Study. 22. Section 10.5 (Study Assessments): added "investigators" to the paragraph on personnel that	between study arms. • Per CIP 4.0, subjects may also complete 48 and 60 months visit remotely per physician's discretion if subjects cannot return to the site for follow-up. The long-term follow-up visits, 48 and 60 months may have higher attrition rate. The remote visit is permitted in the study for 48 and 60 months to keep the attrition rate minimal and be able to collect long term study data as much as			

	can perform Duplex Ultrasound. Updated section on Other Patient- Reported Outcomes on timelines to collect Venous DQoL and timelines for Surgical Stripping Study. Updated section "Questionnaire completion by delegated site personnel" to specify that questionnaires completed by a delegated person might be different and may require EC/IRB approval. 23. Section 10.9 (Index Procedure): updated section Procedure for surgical stripping (CEAP 2-5 subjects in Randomized Studies assigned to surgical stripping). Added language in section Adjunctive Therapies & Treatments on adjunctive therapy and additional treatments as well as on perforating veins. 24. Section 10.10 (Follow-up visits: all Subjects): updated language on Surgical Stripping Study. Added Patient Reported Outcomes and Venous DQoL to the list of assessments, where applicable. Updated language on adjunctive therapies and additional treatments. Added language to perform follow-up at 48 and 60 months remotely. 25. Section 10.12 (Additional Follow-Up Visits: VLU Study Active Ulcers): updated timeline for ulcer assessment. Replaced word "assessment" with "imaging" in section Ulcer Healing Verification Visit.	possible remotely. • Per CIP 4.0 all SAEs will be adjudicated by CEC to ensure better safety oversight. • Per CIP 4.0, the exclusion criteria on COVID-19 has been updated to reflect the current understanding and guidelines. • Data for adjunctive therapies and additional treatments will be collected till 60 months to ensure accuracy of data. • Data on perforating veins for CEAP 4b or 5			

	26. Section 10.13 (Assessment of Effectiveness): updated timelines for Surgical Stripping Study. 27. Section 10.15 (Recording Data): updated section on the CRFs that may be considered source; added VenaSeal system details and AE relatedness. 28. Section 10.17.2 (Study Completed): updated language on Surgical Stripping Study. 29. Section 12.1.1 (Definitions): added definition of U(S)ADE. 30. Section 12.3 (Recording and Reporting of Adverse Events): updated language on reportable events. 31. Section 12.6 (Reporting of Adverse Events): updated language and table on events reporting requirements. 32. Section 13.1 (Clinical Event Committee): added language on adjudication of SAEs and updated name of CRO leading CEC adjudications. 33. Section 14.1.2 (Sample size evaluation on key secondary endpoints): updated text and sample size for Surgical Stripping Study. 34. Section 14.1.3 (Interim Analysis): updated language on Surgical Stripping Study.	target limb are collected from 3 months through study end to perform an accurate healthcare cost analysis. • Investigator reporting requirements updated to reflect the requirements from each country involved in the study. • U(S)ADE definitions was added since this type of events need to be reported according to specific EC/IRB requirements.			

	35. Section 14.2.1 (Sample Size Consideration): language and sample size numbers updated. 36. Section 16.5 (Data Management): changed word "indefinitely" with "in accordance with applicable regulations". 37. Section 18 (Appendices): updated language of question 1 from AVVQ. 38. Administrative updates				
5.0	Updates by section: 1. Cover page: added that Medtronic Bakken Research Center B.V. is EU legal representative. 2. Corrections in table numbering throughout the document. 3. Synopsis: correction in bullet point numbering Secondary Endpoints. 4. Section 6.2 (Rationale): changed "healthcare cost analysis" to "healthcare utilization analysis". 5. Section 9.6 (Exclusion Citeria): correction in bullet point numbering. 6. Section 10.1 (Schedule of Events and Data Collection): Updated Table 7 (Additional Schedule of Assessments – VLU Study) and added the term	Administrative corrections. Clarification of definition Medtronic Bakken Research Center B.V. – EU legal representative.	NA to this version of the template	NA to this version of the template	Marlies de Ligt, Sr. Clinical Research Specialist

	"active" to "Target Active Ulcer Assessment". This was not implemented in version 4.0.				