# Efficacy and Safety of Vascular Boot Warming Program after Acute DVT +/- PE for Earlier Resolution of VTE and Prevention of Post Thrombotic Syndrome: A pilot study.

NCT# NCT03465735

Date: 1/29/2018

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## IRB Minimal Risk Protocol Template

**Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/**

**First-time Use:** Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this template to the protocol section.

**Modification:** To modify this template after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

## General Study Information

**Principal Investigator:** Waldemar E. Wysokinski, M.D., Ph.D.
**Co-Investigators:** Thanila Macedo, M.D.; Mathew Urban, PhD.; and Thom Rooke, M.D.

**Study Title:** Efficacy and Safety of Vascular Boot Warming Program after Acute DVT±PE for Earlier Resolution of VTE and Prevention of Post Thrombotic Syndrome: A pilot study.

**Short Title:** Vascular Boot Warming Program After Acute DVT ±PE

**Protocol version number and date:** Version4.0, 01/29/2018

## Purpose

**Hypothesis:** Early use of a vascular boot warming program plus standard anticoagulation can be a safe and effective method to resolve DVT±PE earlier and prevent development of post-thrombotic syndrome.

**Aims, purpose, or objectives:**

**Primary Objective**

1. The primary objective is to demonstrate whether a vascular boot warming program plus standard anticoagulation over standard anticoagulation can improve resolution of DVT±PE and functional performance in patients with deep vein thrombosis of the lower extremity ± pulmonary embolism.

**Secondary Objectives**

1. Determine if early vascular boot warming plus standard anticoagulation (after 24 hours of anticoagulation therapy from time of diagnosis) is a safe intervention after diagnosis of acute DVT±PE.
2. Determine if vascular boot warming plus standard anticoagulation improves or accelerates the resolution of the clot among those with DVT±PE.
3. Determine if vascular boot warming plus standard anticoagulation improve the venous functional study measures of calf pump ejection fraction, VFR, PDR T90, and overall venous performance score.
4. Determine whether a vascular boot warming plus standard anticoagulation can improve the quality of life in patients with venous insufficiency or previous history of deep vein thrombosis of the lower extremity ± PE.
5. Identify difference in activity level between those who underwent a vascular boot warming program/activity plus standard anticoagulation versus standard anticoagulation only.
6. Analyze whether shear wave elastography will provide a more accurate and reliable method to assess the age of thrombosis and better quantification of thrombosis resolution.
7. Collect natural history data of post-thrombotic syndrome.

**Background:**

Venous thromboembolism (VTE) is a major public health problem with over 500,000 incident or recurrent VTE events occur in the US annually.[1-3] Survival after VTE is reduced, especially after pulmonary embolism (PE). [4] The incidence of VTE in Olmsted County, MN increased by ~5% per decade over the 30-year period, 1981-2010.[5] Anticoagulation for VTE has been the mainstay treatment with little advancement. Unfortunately, acute and chronic venous disorders are extremely common in those that experience VTE. Post-thrombotic syndrome (PTS) is one of the dreaded long-term complications of deep venous thrombosis (DVT). It's been estimated that 1 to 3 of 1000 people in general population is affected by DVT and 25% to 50% patients of patients with DVT develop PTS.[6] The manifestations of PTS can vary from minor leg swelling at the end of the day to severe complications of debilitating limb pain, intractable edema, and leg ulcerations requiring extensive nursing and medical care.[7] It can reduce the patient's quality of life in addition to being a significant financial burden. It is estimated that annually we spend over a billion dollars (up to 2% of the total healthcare budget in all Western countries) on the treatment of chronic wounds. There are still huge gaps in understanding the underlying mechanism and progression of the condition.

Expedient resolution of thrombosis may have a significant impact on PTS. Resolution and recanalization of venous thrombosis generally begins within 1 week of the acute episode.[10] Studies have shown that at least 5% of thrombosed venous segments completely clear within 1 week and 16% to 51% of the cases

resolved within 6 months.[8-10] Killewich et al[9] demonstrated thrombus regression was evident at 1 to 2 weeks and progressed such that only 26% of residual thrombus remained at 24 to 36 weeks. Complete resolution of thrombus occurred in 10 of 18 patients (56%) who completed the 9-month study.

O'Shaunessy et al[8] reported that 60% of their patients had completely resolved their thrombus by the end of 1 year. This study examined 63 above-knee DVT anatomic segments with duplex scanning at 1 week, 1 month, 6 months, and 1 year after the acute event. The segments under investigation were the external iliac vein (EIV), common femoral vein (CFV), superficial femoral vein (SFV), and popliteal vein (PV). Initially, a greater number of segments were occluded (71%) than partially thrombosed (29%). The occluded segments were predominantly in the SFV and PV. At 1 year the thrombi had fully resolved in 60% of the venous segments, 27% remained partially recanalized, and 13% were occluded. At 1-year follow-up the thrombus had fully resolved in 103 segments: 94% of the EIVs, 78% of the CFVs, 42% of the SFVs, and 54% of the PVs. Of these, 61% of the segments were found to be competent without reflux flow, and 39% were incompetent with reflux flow of greater than 1 second. The time involved for individual segments to fully recanalize varied from 1 week to 1 year. Segments that resolved within the first 6 months had a higher frequency of valvular competency than incompetency ($P > .006$). The segments that resolved after 6 months had a higher incidence of incompetency to competency (31:13), but this was not statistically significant. The SFV and PV had a higher incidence of valvular incompetence than the EIV and CFV. All venous segments that were partially recanalized at 1 year were found to have significant reflux. The SFV had the highest incidence of total occlusion at the end of 1 year (36%). Many of the occluded SFVs had established collateral pathways that displayed no evidence of reflux. Ramshorst et al.[11] observed thrombosis resolution to occur in the first 1 to 3 weeks after acute DVT and appeared to occur at an almost exponential rate. They noted that recanalization occurred mainly in the first 6 weeks after diagnosis, but clot resolution eventually occurred in 75% of the thrombosed segments within 6 months. Caprini et al.[12] reported that complete resolution had occurred in more than 40% of thrombosed venous segments within 3 months after the diagnosis of DVT, and lysis had occurred in more than 70% of segments within 6 months of treatment.

To further reduce the VTE burden, better treatments are needed to resolve VTE other than anticoagulation alone. The largest randomized trial to date is the Pulmonary Embolism International Thrombolysis (PEITHO) trial,[13] and resulted in 1,006 patients with acute sub-massive PE-defined as echo evidence of RV dysfunction or positive troponin-to receive anticoagulation with heparin plus tenecteplase or placebo. There was significantly (2.6% vs. 5.6%; P=0.015) lower death or hemodynamic collapse within 7 days and increased rates of intracranial hemorrhage (2.4% vs 0.2%; P=0.003) and major bleeding in the thrombolytic group. The Seattle II study[14] was a prospective, single-arm multicenter trial of ultrasound facilitated, low-dose fibrinolysis for acute massive and sub-massive PE. There was a 25% decrease in CT-measured RV/LV ratio over 48 hours, 0% intracranial bleeding, 2% in-hospital death, and 2.7% 30 day mortality due to catheter-directed low-dose fibrinolysis. The rational for the Seattle II study[14] was to use catheter-directed-low dose fibrinolysis as a disruption device to help dissolve clot. However, there is limited data on the use of vascular boot and warming plus standard anticoagulation in the long term management of patients with DVT and/or PE and its effect on the development of PTS. Warming of the lower extremity enhances blood flow in the treatment of superficial vein thrombosis.

Currently the standard method for diagnosing and evaluating DVT is by 2-D ultrasound with compression and visualization of the vein. Due to the lack of accurate age determination method of DVT, about 30% of DVTs are wrongly staged by using common diagnostic modalities and therefore this leads to therapeutic dilemmas. As thrombus undergoes a stiffening process, the elasticity of the thrombus may serve as a predictor

for the staging of blood clots. Ultrasound elastography is a noninvasive technique to measure tissue stiffness and is a potential technique to determine the age of DVT. When DVT changes due to resolution the function and viscoelastic properties also change. We propose the use of a quantitative, noninvasive method call Shear wave Dispersion ultrasound vibrometry, to measure the viscoelastic properties of the vein.

Instead of studying compressional waves propagation in the MHz range, other approaches to study the mechanical properties of soft tissues have used shear waves at low frequencies (typically ranging from 50 Hz to 1000 Hz) (Muthupillai et al. 1995; Sarvazyan et al. 1998). Gennisson et al. in 2006 and Schmitt et al. in 2011 used mechanical vibrators to generate shear waves in the blood samples, allowing the study of the dynamic process of blood coagulation (Gennisson et al. 2006) and the comparison of different rheological models (Schmitt et al. 2011). Another approach using radiation force was described by Viola et al. in 2010 in which they used the ultrasound push to move the blood clot and measured the displacement generated. This technique was used tomeasure the change in relative compliance of ex vivo clots as they were formed (Viola et al. 2010). Even though it has been shown that the composition of blood clots is not homogenous (Taber et al. 1996), to our knowledge there are no studies describing the elastic properties of blood clots.

Therefore, there is a real interest in a noninvasive technique for the study of two-dimensional (2-D) elasticity properties of blood clots. This technique could be used to diagnose the age of thrombi, stratify the resolution of blood clots and help understand the coagulation process from a mechanical standpoint. It could also potentially be used to monitor the effect of therapies that are currently used on the clot elasticity.

**Study Rationale Innovation and significance:**

Warming of the lower extremity enhances blood flow in the treatment of superficial vein thrombosis and has been well established.[16] However, the effect of vascular boot warming plus standard anticoagulation on deep venous disease progression is unknown and may prove to reduce DVT with standard anticoagulation more effectively and quicker with reduced risk for PTS. To date, there is no randomized control study evaluating the effect of vascular boot warming plus standard anticoagulation in venous insufficiency. We hypothesize that the combination of vascular boot warming and standard anticoagulation will result in improvement in calf muscle pump function, thus improvement in venous physiology and quicker resolution of DVT and associated clinical symptomatology of post thrombotic syndrome. Ultrasonography with shear wave elastography imaging is a novel ultrasound technology that potentially can quantify and assess thrombosis age, evolution of thrombosis, and risk of detachment. These evaluations can be readily performed in the patient's examination room on a single ultrasound system. The overall anticipated results of our research proposal are to demonstrate that: 1) DVT may resolve more effectively with a vascular boot through warming evaluated by standard 2-D ultrasonography with compression (standard therapy); 2) shear wave elastography is a feasible diagnostic tool in those with lower extremity thrombosis; 3) shear wave elastography can provide a more accurate and reliable method to assess the age of thrombosis and better quantification of thrombosis resolution while assessing the natural history, progression, and risk of detachment; 4) this technology can readily be incorporated into the daily workflow to improve diagnostic and prognostic value for detection of DVT and resolution [It has been estimated that the average image acquisition time to be added to a standard ultrasound study is minimal (7-10 minutes for shear wave elastography imaging) 5) these techniques can improve prediction of complications among those with DVT and; 6) these techniques can help decrease the number of age indeterminate thrombus that may result in unnecessary treatment with anticoagulation and its associated risks.

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**Subject Information –** charts, records, images, or specimens are considered 'subjects'

*Target accrual is the proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens,* ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

**Target accrual:** 30 patients (15 patients with vascular boot vs 15 patients without vascular boot)

**Subject population:**
All patients diagnosed with acute lower extremity DVT per ultrasound ± pulmonary embolism (PE) per computed tomography scan seen in the Thrombophilia clinic or Mayo Hospital for start of anticoagulation will be approached for participation in the study.

**Inclusion Criteria**

1. Age ≥18
2. Able to tolerate wearing a vascular boot, if randomized to this group.
3. Diagnosis of acute DVT±PE (within 24 - 48 hours) and received approximately 24 hours of anticoagulation prior to starting the study.

**Exclusion Criteria**

1. Unable to tolerate wearing a vascular boot
2. Unable to comply with keeping log of activity/ of wearing a vascular boot.
3. Weight > 300 pounds. *(weight limit for the venous plethysmography chair)*
4. Previous history of DVT or PE.
5. On anticoagulation for another purpose (example stroke prevention with atrial fibrillation).
6. Patients who do not accept to participate in research studies.
7. Pregnant women will not be allowed to participate
8. Patients less than 18 yrs

☐ Yes ☒ No Will a Certificate of Confidentiality (COC) be obtained from NIH?

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## Study Design

### Methods

Patients with diagnosis of acute lower extremity DVT (proximal and distal) and/or pulmonary embolism will be identified and approached for participation, when they are seen in the Thrombophilia Clinic or Mayo Hospital for management of the acute VTE. If they match the preset inclusion and exclusion criteria, they would then be consented during this visit and scheduled for baseline studies at a later date.

**Baseline studies will include:**
(1) Venous plethysmography: (ejection fraction, VFR, PDR T90, EDV T90, MV, F1.0).
(2) Lower Extremity Ultrasound: DVT (thrombus) evaluation with 2-D ultrasonography (standard) and shear wave elastography (done within 1 day of baseline clinical ultrasonography).
(3) Other relevant clinical information (such as height, weight, BMI, bilateral calf circumference, edema, leg pain, ulcerations, previous LE surgery, use of compression stockings, and any current set exercise program). Demographical data, common vascular risk factors (including tobacco use, coronary and peripheral arterial occlusive disease, diabetes, hypercholesterolemia, and hypertension) and the treatment information, will be obtained from chart review via ACE database and Synthesis. All data will be entered and stored in RedCap research tool.
(4) Anatomic distribution of thrombi at initial examination will be documented as single segment and/or multi-segment(s) involved. The segments will be label as: external iliac vein (EIV), only if clot extends above the common femoral vein; common femoral vein (CFV); femoral vein (FV) (upper, middle, lower); deep femoral vein (DFV); popliteal vein (PV); posterior tibial vein (PTV); gastrocnemius (G-calf); peroneal vein-calf (PV-calf); soleal vein-calf (SV-calf) (see Table 1).

Table 1.0

| Site | Anatomic Distribution of Thrombi | | | |
|---|---|---|---|---|
| | **Initial** | **3 days** | **10 days** | **3 months** |
| **Single Segments** | | | | |
| External Iliac (EIV); if evaluated | | | | |
| Common femoral (CFV) | | | | |
| Femoral- Upper (FV) | | | | |
| Femoral - Middle | | | | |

| | | | | |
|---|---|---|---|---|
| Femoral - Lower | | | | |
| Deep Femoral (DFV) | | | | |
| Popliteal (PV) | | | | |
| Posterior Tibial (PT-calf) | | | | |
| Gastrocnemius (G-calf) | | | | |
| Peroneal (P-calf) | | | | |
| Soleal (S-calf) | | | | |
| **Total** | | | | |
| **Multisegment** | | | | |
| EIV- CFV | | | | |
| EIV- CFV-FV | | | | |
| EIV- CFV-FV-PV | | | | |
| EIV- CFV-FV-PV-calf | | | | |
| CFV-FV | | | | |
| CFV-FV-PV | | | | |
| CFV-FV-PV-calf | | | | |
| FV-PV | | | | |
| FV-PV-calf | | | | |
| **Total** | | | | |

Patient will then be randomized to vascular boot plus standard anticoagulation program or standard anticoagulation using the randomizer built into RedCap.

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**Standard of Care (SOC) Group (no vascular boot utilized)**: Patients will receive standard anticoagulation (determined at discretion of the treating provider), baseline studies, and follow up at the end of treatment (3months).

**Vascular Boot (VB) Group (includes vascular boot in addition to SOC)**: Patients will receive standard anticoagulation (determined at discretion of the treating provider), baseline studies and standardized vascular boot warming (see below). All patients randomized to this group will wear the vascular boot for a minimum of 30 minutes per day for the first 10 days of participation. Patients in this group may initially be enrolled at either the thrombophilia clinic or the hospital.

**Standardization of the vascular boot warming:**
The vascular boot is designed to completely surround the foot, heel and calf, insulating the limb. For each vascular boot session, the following data will be recorded:
(1) Total duration of wearing vascular boot during first 10 days of study participation
(2) Affected leg pain measured on a 0-10 scale at initial vascular boot warming (baseline) and every day during the calf warming while participating in the study.

**Follow up data (SOC and VB Groups) include:**
(1) Ultrasound of the leg with DVT and leg circumference measurement at 3 days, 10 days, and 3 months. Ultrasound data will include data on thrombus resolution, such as size and recanalization present.
(2) Venous plethysmography at 3 months.
(3) Study Questionnaires:
   a. Godin questionnaire (validated questionnaires to measure physical activity)
   b. VEINES-QOL (generic physical quality of life questionnaire)
   c. Villalta Score (to assess Post-Thrombotic Syndrome)

**Ultrasound Measurements and Criteria:**
The criteria for complete occlusion (occlusive) were absence of flow with distal augmentation and incompressibility of the vein. Minimal clot will be defined by wall thickening, webbing, etc. Partial recanalization will be defined by >50% or <50% normal or diminished flow with distal augmentation and partial incompressibility of the vein. Complete recanalization (resolved or no clot) will be defined by spontaneous phasic flow and a completely compressible vein and no residual clot (see Table 2).

Table 2.0

| **Site** | **No Residual Clot** | **Minimal Clot (wall thickening, webbing, etc)** | **Recanalized >50%** | **Recanalized <50%** | **Near Occlusive** | **No Change** | **Worse Or Extension** |
|---|---|---|---|---|---|---|---|
| External Iliac (EIV);<br><br>if evaluated | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Common femoral (CFV) | | | | | | | |
| Femoral- Upper (FV) | | | | | | | |
| Femoral - Middle | | | | | | | |
| Femoral - Lower | | | | | | | |
| Deep femoral (DFV) | | | | | | | |
| Popliteal (PV) | | | | | | | |
| Posterior tibial (PT-calf) | | | | | | | |
| Gastrocnemius (G-calf) | | | | | | | |
| Peroneal (P-calf) | | | | | | | |
| Soleal (S-calf) | | | | | | | |
| Total | | | | | | | |

**Study Procedure**

All subjects included in this study will have a diagnosis of deep vein thrombosis that will undergo standard anticoagulation with or without wearing a vascular boot. Medical charts will be abstracted for clinical, laboratory, medications, imaging and pathologic findings. Subjects will undergo their initial (baseline) clinically indicated DVT ultrasound for diagnosis of lower extremity DVT. The second clinically indicated limited venous ultrasound will be completed on post-DVT day 90 (14±days) to evaluate resolution. Research ultrasound intervals will then occur on days 0 (+1 days), 3 (-2/+5 days), 10 (±5 days), and 90 (14±days). Shear wave elastography will be conducted at all post-treatment ultrasound intervals. We will compare the shear wave elastography to the opposite lower extremity veins on the same individual for a control if DVT is not present in that extremity at that time or previously.

Commercially available ultrasound systems (Logiq E9, GE Medical Systems, Milwaukee, WI, USA) equipped with phased-array and linear transducers will be utilized. Longitudinal and short axis images of each clot will be acquired and digitally stored for offline analysis. The short axis images will be acquired. 2-D images, 2D shear wave and elastography images will be acquired and digitally stored for off-line analysis. All measurements will be made in a blinded fashion by a single observer.

**Shear Wave Elastography:** The subject will be asked to lay on a hospital bed for ultrasound imaging. The veins of the lower extremity will be visualized using ultrasound imaging, and the depth of the venous wall will be noted. The focal depth on the device will be set to measure shear wave propagation in the walls of the vein and in the thrombus. Measurements will be made at multiple locations along the veins length.

**Human Subjects**

Recruitment of Subjects: Informed written consent will be obtained prior to the participation in the study and recorded in clinical documents as per Institutional stipulations. Each patient will be contacted by the principal investigator or IRB approved designees. The potential risks to participants will be minimal. The ultrasound output level used in this study is well under the current FDA safety limits for diagnostic ultrasound. No additional drugs or invasive procedures will be used in their study. The decision to participate in this study or not will not affect the treatment of patient subjects. This study involves minimal risk to the patients. All participants included in this study must have given authorization for use of their medical records in research. All subject data will be collected, reviewed, and protected according to current HIPAA regulations and as stipulated by the IRB. The data will be analyzed anonymously and all results will only be published in aggregate.

Resources:

- Funding for the vascular boot and vascular studies (ultrasound, venous plethysmography) will be through the Vascular Center research fund.

**Check all that apply. If none apply, leave blank:**

☐ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement*.

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☒ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☐ The study involves photographing, audiotaping or videotaping subjects (and guests).

## Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

☐ **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)_____

## Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. *Example: 01/01/2000 to 12/31/2013* or all records through mm/dd/yyyy.

For a retrospective chart review, enter the date range:

**Check all that apply**:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

☐ This study involves only data and/or specimens that will be collected after submission to the IRB.

☒ The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained. When appropriate, check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol*.

IRB Number/s - Data Only: _____

IRB Number/s - Specimens Only: _____

IRB Number/s - Data and Specimens: _____

Note: When subjects provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study, e.g. receiving data/specimens from an external party. When checked, provide all data sources:

## Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

**Subject Identifiers**: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

**Internal** refers to subject identifiers that will be included in the dataset maintained by the study team.

**External** refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

| **SUBJECT IDENTIFIERS**<br>**Check all that apply** | INTERNAL IDENTIFIER | EXTERNAL IDENTIFIER |
|---|---|---|
| Name | X | |
| Social Security number | | |
| Medical record/patient registration number, lab accession, specimen or radiologic image number | X | |
| Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data | X | |
| Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. | X | |

| | | |
|---|---|---|
| **Note:** Recording a year only is not a unique identifier. | | |
| Medical device identifiers and serial numbers | | |
| Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images | | |
| Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address | | |
| Street address, city, county, precinct, zip code, and their equivalent geocodes | X | |
| Phone or fax numbers | X | |
| Account, member, certificate or professional license numbers, health beneficiary numbers | | |
| Vehicle identifiers and serial numbers, including license plate numbers | | |
| **If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".** | ☐ None | ☐ None |

## Statistical Information

*Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies*.

☐ No statistical information.

**Statistical Considerations**

**Data Analysis Plan:**
This is a pilot study including 30 volunteers. Sample size cannot be calculated statistically due to lack of prior studies in the literature for those with DVT and use of warming boot. We will recruit up to 30 subjects who have valid measurements as described in the Data Analysis plan.

The ultrasound measurements (elastography) will be assessed for validity using data analysis techniques and to examine the visualization of the venous wall to see if we can quantify the thrombosis.

All statistical tests will be 2-tailed at a significance level of $P<0.05$. Demographic and physical characteristics laboratory values and comorbid conditions will be presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Counts and percentages will be presented for categorical variables, while means ±standard deviations and 95% confidence intervals will describe continuous variables for which normality assumptions are met. If the distribution of a continuous parameter is skewed, transformations will be considered, or medians and interquartile ranges (IQR) will be presented. Continuous variables will be compared between 2 groups using unpaired t-tests. For comparison of continuous variables in ≥3 groups, one-way analysis of variance (ANOVA) followed by a Scheffé test may be performed. Frequencies will be compared using Chi square analysis. The correlation between 2 continuous variables will be determined using a linear regression analysis. Cox proportional hazards regression will be used to estimate the

association between thrombosis and short-term and long-term outcomes. Logistic regression will be used to estimate the association between thrombosis and binary outcomes. Adjustment for potential confounders will be accomplished through, either, covariance regression modeling, propensity score stratification, or propensity matching, according to the discretion of the statistical analyst. Statistical analyses will be performed using SAS and/or R software.

## Endpoints

**Primary:**
Early resolution of the DVT±PE as measured by the ultrasound. Partial recanalization will be defined by normal or diminished flow with distal augmentation and partial incompressibility of the vein (>50% or <50%). Complete recanalization will be defined by spontaneous phasic flow and a completely compressible vein.

**Secondary:**

i. Improvements in calf muscle function as measured by venous plethysmograthy (ejection fraction, VFR, PDR T90, EDV T90).
ii. Improved quality of function : Godin questionnaire (validated questionnaires to measure physical activity), VEINES-QOL (generic physical quality of life questionnaire) and Villalta Score (to assess Post-Thrombotic Syndrome)
iii. Analyze whether shear wave elastrography will provide a more accurate and reliable method to assess the age of thrombosis and better quantification of thrombosis resolution.

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