Cover Page

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Document:
Study Protocol & Statistical Analysis Plan

Official Study Title:
Role of a Novel Exercise Program to prevent Post Thrombotic Syndrome (EFFORT-2)

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Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Despite standard care, 25%-50% of patients with clots in the deep veins of the arms and legs progress to chronic post-clot problems resulting in significant disability, loss of productivity, and healthcare costs. Reverse flow in the veins from an organizing clot is the primary cause of post-clot problems. Veins with early clot breakdown have a lower incidence of reverse flow. We have observed that clot breakdown is enhanced by increased blood flow and that moderate arm and leg exercise results in increased venous blood flow. Hence, we predict that a supervised exercise program in patients with deep vein clots could increase leg vein blood flow, accelerate clot breakdown, and decrease the risk of post clot problems. The primary hypothesis is that increased blood flow across the clot (induced by supervised exercise) will increase clot breakdown and decrease severity of post clot problems. The overall purpose is to determine whether a progressive exercise training program can lower the risk of post clot problems in patients with sudden deep vein clots, and to investigate possible ways by which this occurs. We propose a randomized clinical trial of standard therapy compared to progressive exercise training in patients with leg deep vein clots.

Aim 1 will test whether a 3-month exercise training program increases vein blood flow, improves clot break down, and prevents post-clot problems over 2 years of follow-up. Patients with deep vein clots in the leg will be randomized to standard therapy alone (blood thinning medication, compression stockings on the legs, and movement allowed at will), OR to exercise plus standard therapy. 260 patients will be enrolled in this study.

Aim 2 will investigate ways by which the exercise program may act to prevent post clot problems.

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

Standard anti-coagulation therapy for acute deep vein thrombosis (DVT) reflects the current short term focus on preventing pulmonary embolism (PE) and recurrent DVT. Despite standard care, 25% to 50% of patients with DVT progress to the chronic post-thrombotic syndrome (PTS) resulting in significant disability, loss of productivity, and healthcare costs.

Venous valvular reflux resulting from chronic injury and entrapment by an organizing thrombus is the primary cause of PTS. Patients with spontaneous early thrombus resolution have a lower incidence of valvular reflux. We have observed that venous thrombus resolution is enhanced in a mouse model of thrombosis with increased blood flow, compared to models with reduced flow or no flow. Our pilot work in humans confirms that brief periods of moderate upper or lower extremity exercise result in increased blood flow in the iliac veins. Hence, we postulate that a supervised exercise program in patients with acute DVT could increase lower extremity venous flow, accelerate thrombus resolution, and thereby decrease the risk of PTS.

The primary hypothesis of this proposal is that increased blood flow across the thrombus (induced by supervised exercise) will accelerate thrombus resolution and decrease the prevalence and severity of PTS. However, exercise does have additional physiologic actions that may enhance thrombus resolution. We have found that exercise increases systemic fibrinolytic activity and circulating endothelial progenitor cells. The overall purpose of this proposal is to determine whether a progressive exercise training program can lower the risk of PTS in patients with acute DVT, and to investigate possible mechanisms by which this occurs.

The potential benefit of supervised exercise in preventing PTS has not been systematically studied in patients with acute DVT, perhaps for fear of causing a new DVT or PE. However, randomized and cohort studies confirm the safety of ambulating patients as early as 24 hours after acute DVT, suggesting that early moderate gradually escalating exercise prescriptions might be tolerated. Furthermore, progressive exercise training is widely endorsed in cardiovascular patients that were also considered high-risk in the past. There could be substantive functional, health and economic benefit if exercise therapy were to show even modest efficacy in reducing PTS in patients recovering from DVT. We propose a randomized clinical trial of patients with acute lower extremity DVT undergoing standard therapy alone (anticoagulation, compression, ambulation ad-lib) , VERSUS exercise plus standard therapy to determine the following:

Aim 1 will test whether a 3-month exercise program has long-term clinical benefits in acute DVT. The primary outcome measures will be Villalta score for PTS and VEINS-QOL score (Venous Insufficiency Epidemiological and Economic Study-QOL) for venous quality of life at 2 years of follow-up.

Aim 2 will evaluate whether exercise therapy in patients with acute DVT enhances thrombus resolution through increased fibrinolysis and venous flow. Fibrinolysis (blood plasminogen activator inhibitor-1 [PAI-1] and tissue-type plasminogen activator [t-PA]), post-exercise venous volume flow, and percent change in thrombus volume will be measured at regular intervals as specified in the schedule of events.

Aim 3 will assess the relationship between PTS, venous hemodynamics and exercise capacity. It will test whether exercise improves venous hemodynamics (valvular reflux, and calf muscle pump function) by enhancing functional capacity (lower extremity muscle strength, flexibility, and aerobic capacity).

Collectively, the proposed studies will define the role of increased blood flow as a novel therapy to accelerate thrombus resolution and prevent PTS. We will also define the effects of exercise on systemic inflammation, fibrinolytic and vascular repair, calf muscle pump action, and functional ability in patients with venous thrombosis.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

This is a prospective, randomized, controlled, unblinded trial enrolling 260 patients with acute DVT to either standard care alone (anticoagulation, compression, ambulation ad-lib) or standard care plus a 3 month exercise program. Patients will be followed for 2 years. Patients with acute DVT will be randomized to their assigned treatment groups and undergo baseline study evaluations. The Villalta score for PTS and QOL measures will serve as the primary and secondary endpoints respectively. Testing for venous flow, thrombus resolution, venous hemodynamic function and functional capacity will be performed serially.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

The continued presence of thrombus within the venous system after acute DVT is an important risk factor for PTS. Despite adequate anticoagulant and compression therapy, incomplete clearance of thrombus after acute DVT is common. PTS develops more frequently in DVT patients that have residual venous thrombus (47% vs. 23%, $p \leq 0.01$). Conversely, valvular reflux and PTS develop much less frequently in veins with rapid thrombus resolution (26-35% vs. 61-80%, $p \leq 0.005$). Disturbed venous blood flow with attendant low shear rates resulting from venous reflux, outflow obstruction, and/or stasis leads to venous thrombosis. This explains the efficacy of sequential compression devices (that intermittently increase lower extremity venous flow) in preventing venous thrombosis. We show a novel finding in that enhancing venous flow not only prevents thrombus formation, but also enhances thrombus resolution in both animals and humans.

Supervised exercise therapy has not been implemented in patients with acute DVT perhaps for fear of causing a new DVT or dislodging an unstable thrombus and causing a PE. In fact, patients with acute DVT were traditionally treated with strict bed rest for the first 5-10 days. However, at least 7 randomized controlled trials (RCTs) and additional cohort studies confirm that early ambulation after the diagnosis of DVT does not increase the risk for PE. There may in fact be a reduced risk of PE and an improvement in leg pain/swelling. In the current (American College of Chest Physicians' (ACCP) guidelines "early ambulation in preference to initial bed rest" is a Grade 1A recommendation for acute DVT.

Regular exercise activates systemic fibrinolysis cascades while significantly strenuous exercise (e.g. marathon running) generates a procoagulant profile. We have found that even a single bout of low-moderate intensity treadmill walking in elderly patients with cardiovascular disease results in increased tPA activity and reduced PAI-1 activity. In fact, a 20 minute exercise training program elicited a larger response than an equicaloric but longer program.

Calf muscle pump function is dependent on the contractile ability of the gastro-soleus muscle complex. Calf strengthening exercises improve pump function and alleviate symptoms in patients with established pump failure such as chronic venous diseases, including patients with established PTS. The limited mobility associated with ankle fractures is associated with significant venous dysfunction while improved ankle flexibility results in improved calf muscle pump function with improvement in venous function.

There are no studies that have evaluated whether supervised exercise training prescribed in the acute phase of DVT will lyse the thrombus, preserve venous hemodynamics, prevent pump failure and reduce long-term complications in these patients.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Chronic sequelae of acute DVT. DVT is traditionally viewed as an acute condition with a high risk of pulmonary embolism (PE), followed by a progressively reducing risk of adverse events over time. Early diagnosis and effective anticoagulation can prevent PE and acute mortality. Anticoagulation does not accelerate thrombus resolution which can result in chronic sequelae.

A significant proportion of patients with PE have residual organizing thrombus leading to macrovascular obstruction, small-vessel arteriopathy, and vasoconstriction. As many as 10% of such patients will develop pulmonary artery hypertension with hypoxemia and progressive right heart failure. The only effective treatment for this chronic thromboembolic pulmonary hypertension (CTPH) is thromboendarterectomy, a major operation with high peri-operative mortality (5% to 10%).

Incomplete clearance of thrombus in the lower extremities after acute DVT is extremely common. Failure of complete resolution can trap venous valves in an organizing thrombus causing valvular reflux. Residual thrombus may also organize and cause vein wall stricture (obstruction). Reflux or obstruction leads to venous hypertension and calf muscle pump failure with consequent post thrombotic syndrome (PTS). PTS is characterized by chronic limb pain and swelling progressing to venous claudication, dermatitis, fibrosis, and skin ulceration. Graduated elastic compression stockings and early ambulation after acute DVT can reduce the incidence of PTS and are Grade 1A recommendations by the American College of Chest Physicians (ACCP). Despite optimal therapy, 25% to 50% of patients develop PTS within two years after symptomatic DVT with as many as 1/3rd progressing to venous ulcers. Since there is no cure for PTS, patients can only be managed with supportive care. There are over 500,000 patients with PTS in the United States.

Clearly, achieving the “modern” therapeutic goal still does not provide optimal clinical outcomes for a large subset of patients with DVT. The treatment of DVT needs to be expanded substantially to include the prevention of health and functional impairment caused by the post-thrombotic syndrome (PTS). There is a clinical need to identify more effective methods of preventing PTS and its accompanying morbidity, disability, and economic burden. We propose to address this clinical need by evaluating the potential benefit of a unique progressive exercise rehabilitation program as an adjuvant to current acute DVT therapy to prevent PTS and improve QOL. Similar exercise programs that are widely used in the rehabilitation of cardiac and arterial diseases may be helpful in chronic venous disease, yet have not been systematically evaluated in acute venous thrombosis. Understanding the efficacy of exercise for reducing PTS and its complications may lead to the incorporation of exercise rehabilitation into standard care for DVT, significantly improve health and QOL, and have implications in the prevention of CTPH.

How big is the problem? Quality of life (QOL). PTS affects ambulatory ability resulting in severe limitations in daily activities. PTS also leads to venous leg ulcers that are difficult to treat and often recur. The reduction in QOL is similar to that of patients with chronic heart, lung, or arthritic disease. PTS is the leading predictor of QOL two years after a DVT episode when the SF-36 questionnaire is used to measure generic QOL and the VEINES-QOL questionnaire is used to measure venous disease specific QOL. Patients with PTS have worse health perceptions, physical functioning, and role limitations on the SF-36. Almost 90% of patients are disabled or unable to work because of leg symptoms ten or more years after iliofemoral DVT.

Economic impact. PTS imposes a large cost on society from direct health care expenditures, as well as lost productivity. In one study, the annualized median cost for treating PTS was $20,569, while the additional cost of treating venous ulcers was estimated to be $10,000 per patient per year. The direct cost of treating PTS exceeded $300 million per year in the 1990s and is likely now well over $1 billion. The indirect costs of PTS are also substantial, since it often affects persons of working age. 2 million workdays are lost annually in the US from leg ulcers alone.

Economic impact of this study. About 350,000 to 600,000 individuals develop DVT every year. If our proposed intervention of supervised exercise therapy reduces the risk of developing PTS in these patients by even 10% (our anticipated effect size with exercise is larger) this will translate into a savings of $58 million/year [(10/100) X 500,000 X 11,667]. Therefore the total cost of the proposed study could be returned in ~13 days of public health cost savings related to PTS. If our proposed intervention reduces the loss of workdays from established PTS, this will result in additional savings.

Innovation. As a practicing vascular specialist, I encounter the devastating and intractable sequelae of DVT in the form of PTS on a daily basis but can only provide supportive care since there is no definitive cure. Results of this study will have a direct impact on this currently untreatable condition. Moreover, results from this study will have implications for the management of chronic thromboembolic pulmonary hypertension (CTPH) and other venous thrombotic conditions.

Multiple lines of evidence suggest that increased flow may be a logical mechanism to exploit for acceleration of thrombus resolution in acute DVT. This proposal will be the first human application of a standardized exercise training program designed to safely increase venous flow and enhance thrombus resolution. It is also the first human study to test the hypothesis that accelerated thrombus resolution prevents PTS. The exercise program will be implemented for the first 6 months with an anticipated improvement in PTS incidence and severity manifested 2 years later. Implicit in this hypothesis is the novel concept that by accelerating thrombus resolution in the early course of DVT, exercise will be able to alter the natural history and trajectory of PTS over the long-term.

The study translates observations made in the laboratory on thrombus resolution in mouse models into the clinical arena. By asking mechanistic questions, it provides the most comprehensive physiologic evaluation of the therapeutic effects of exercise on acute DVT. While exercise consistently increases venous flow, we are aware of the fact that it has many systemic and cardiovascular benefits that may also impact thrombus resolution or calf muscle pump function, both of which may in turn affect the risk for PTS. These benefits of exercise will also be tested for the first time in the context of DVT and PTS. Finally, the study will also provide novel information on the associations between thrombus resolution and endothelial progenitor cells. Our protocols place emphasis on enhancing venous flow, fibrinolysis and the calf muscle pump, but should also be viewed as potentially efficacious in the larger context of improving general functional capacity. In other words, free-living physical activity patterns outside of structured exercise sessions could be enhanced to such a degree by general fitness and functional improvements that PTS incidence and symptoms will be indirectly affected.

We have also introduced several methodological innovations. While even mild unsupervised ambulation reduces thrombus progression in acute DVT and poses no risk for PE, we have carefully developed a unique exercise program that involves upper arm activity in the first week, then progressively involves the lower extremities as tolerated. Our development and application of unique 3D thrombus volume reconstructions and quantification of recanalization in vivo are highly innovative and have never been applied to thrombus in humans. Similarly, our in vivo vein wall elasticity technique will generate novel biomechanical data over the course of thrombus resolution in humans. These innovative clinical measures, developed and refined by our group, are being used for the first time in the context of DVT. Our results have the potential to revolutionize the assessment of acute DVT patients and their risk stratification for future PTS as these innovative protocols are incorporated into clinical practice.

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

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2 If available, upload your applicable literature search:

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Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

Study Visit Windows:

Baseline visit must occur within 28 days from the diagnosis of the DVT
1 Month visit ± 7 days
3 Month visit ± 14 days (optional visit)
6 Month visit ± 14 days (optional visit)
1 Year visit ± 28 days
2 Year visit ± 56 days

In response to the COVID-19 pandemic, participants will have the option of telehealth visits if they are unable to come onsite for follow-up visits.
Telehealth visits will include medical history, questionnaires, and Villalta through VA approved communication platform (Apple FaceTime, Facebook Messenger video chat, Google Hangouts video, Skype, or WhatsApp). Questionnaires (with no PII or PHI) may be mailed to the participants with pre-stamped/pre-addressed envelopes for completion at the participant's homes. To better document Villalta testing during a telehealth visit, a photograph/shot will be taken of the affected lower extremity through the selected communication platform.
Patients choosing to continue to come onsite will complete medical history, questionnaires, Villalta, exercise testing, and ultrasound imaging, described below.

The following study related activities will be preformed/conducted at UMMC:

3D Ultrasound for thrombus volume, vein wall elasticity, and venous flow. The non-invasive test will be performed while lying down with minimal discomfort using a clinical ultrasound machine.

The following study related activities will be preformed/conducted at VAMHCS:

Questionnaires for Quality of Life (VEINS-QOL & SF-36), post thrombotic syndrome severity (Villalta score). There are no significant risks to the subjects, except for potential anxiety while answering questions regarding their symptoms and signs. Every effort will be made to ensure patient comfort during the testing.

Blood draw (10 teaspoons) for markers of fibrinolysis, inflammation and angiogenesis. This may be accompanied by minor discomfort such as pain, bruising and bleeding. Phlebotomy will be explained carefully and will be conducted according to clinical standard of care using standard aseptic technique.

Supervised upper and lower body exercise:

Exercise Phase 1 (Day 1 - Day 7/Discharge): After initiation of anticoagulation therapy, we will begin upper body exercise that will last approximately 7 days of the patient's hospital admission or until the patient can safely ambulate or until the patient is discharged, if that is earlier than 7 days.

A) For those patients admitted to the hospital: Subjects will complete 2 daily sessions of bedside exercise on a portable upper body ergometer. Each session will consist of three intermittent 30-second bouts of upper body cycling at approximately 5W and 75-85 rpm; each bout will be followed by a 10 minute rest period.

B) If the patient is unable to perform upper body ergometry, NMES will be used to induce contraction of the plantar flexors and dorsi flexors of both lower extremities. The FDA has cleared the device for this purpose. This device is routinely used in clinical care and has been used in other studies at UMB. Electrodes will be placed over the plantar and dorsi flexors of each leg. The stimulator's parameters setting will be adjusted to elicit contraction while maintaining participant comfort. Stimulation will be provided for approximately 15-30 minutes daily as tolerated by the participant

Exercise Phase 2 (Day 7/Discharge–Month 1): Phase 2 will begin immediately after discharge. Subjects will perform aerobic exercise (supervised treadmill walking) at the VA facility once a week and will walk twice a week at home (for a total walking exercise of 3 times a week). Participants do not have to come to the VA gym on a weekly basis and can choose to exercise at home only. If participants choose to exercise at home only, they will be required to walk at least 3 times a week and will receive weekly phone calls to assess safety and compliance. The research team will determine if the participants should continue exercise or refrain from research exercise until medically cleared. If determined that the participant should refrain from exercise, they will be instructed not to exercise until the research team discusses and informs the participant it is safe to exercise.

Participants will be informed that if they have a medical event requiring hospitalization or treatment of some kind, to refrain from the study exercise program until they speak with the study team and/or are given medical clearance by the treating clinician or primary care physician.

Training on the treadmill will start at a very low intensity (approximately 40-50% age-predicted heart-rate [HR]-reserve for 20 min) and progress to approximately 60-70% HR-reserve for 30 minutes during the first 3-4 weeks based on each subject's tolerance. Subjects will also begin a supervised flexibilty training program consisting of a stretching regimen with a focus on improving knee and ankle flexibilty. After each aerobic exercise session subjects will perform 8 lowerbody stretching exercises (1- dorsiflexion, 2- strainght leg plantar flexion, 3 -bent knee plantar flexion, 4- knee flexion, 5- hip extension, 6- hip abduction, 7- hip adduction, 8- hamstring stretch). Subjects will repeat the same exercise regimen at least 4 days per week at home. Exercise intensity will be monitored using heart rate monitors . Subjects will be encouraged to achieve the prescribed target HR while walking at home and will be given a HR monitor. Thus, we will have objective and quantifiable data on compliance to the exercise program. The research coordinator will track each patient. We will provide subjects with an exercise logbook to maintain, which will be reviewed weekly by study staff. We will download HR data periodically for review.

If the patient is unable to perform walking exercise, NMES will be used to induce contraction of the plantarflexors and dorsiflexors of both lower extremities as described above. Participants will be taught how to safely use the device and take the device home to use. If a participant becomes able to perform walking exercise, he or she will be transitioned to the aerobic exercise described above.

All subjects will also begin a supervised flexibilty training program consisting of a stretching regimen with a focus on improving knee and ankle flexibilty. After each aerobic exercise session subjects will perform 8 lowerbody stretching exercises (1- dorsiflexion, 2- strainght leg plantar flexion, 3 -bent knee plantar flexion, 4- knee flexion, 5- hip extension, 6- hip abduction, 7- hip adduction, 8- hamstring stretch). Subjects will repeat the same exercise regimen at least 4 days per week at home.

Exercise Phase 3 (Month 2- Month 3): Subjects will continue their weekly supervised exercise at the VA facility (1 x 30min/week @ approximately 60-70% HR-reserve), but will extend the walking program at home to 4 days per week. As before, compliance will be documented through the heart rate monitor and an exercise log book maintained by the participant and verified by study staff.
Participants do not have to come to the VA gym on a weekly basis and can choose to exercise at home only.
If participants choose to exercise at home only, they will be required to walk at least 5 times a week and will receive weekly phone calls to assess safety and compliance. The research team will determine if the participants should continue exercise or refrain from research exercise until medically cleared. If determined that the participant should refrain from exercise, they will be instructed not to exercise until the research team discusses and informs
the participant it is safe to exercise.

Participants will be informed that if they have a medical event requiring hospitalization or treatment of some kind, to refrain from the study exercise program until they speak with the study team and/or are given medical clearance by the treating clinician or primary care physician.

B) If the subject is performing passive (NMES) exercise, they will continue, but will increase the frequency to 5 days per week.

Exercise Testing: Subjects will undergo a 400 meter walk test, wherein time to walk 400 meters is measured. Subjects are instructed to walk as quickly as possible over a flat surface of premeasured distance, while timed by a stop watch. The 400 meter walk is strongly correlated with peak VO2 and may be a better measure of capacity than specific time to walk tests (Simonsick EM, J Am Geriatrics Soc 54:127-132) . We will also measure plantar flexion strength using a hand held dynamometer.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):
Physical examination for DVT risk factors and venous disease severity assessment
Duplex ultrasound for diagnosis of DVT
Anticoagulation (per treating physician recommendations; not altered by the study)
Compression stockings

3 * Describe the duration of an individual participant's participation in the study:
All enrolled subjects are expected to participate in the study for two years

4 * Describe the amount of time it will take to complete the entire study:
The study will conclude enrollment and follow-up activities by 6.30.2020

5 * Describe any additional participant requirements:
No additional participation requirements.

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

For the randomized trial, we have calculated sample size based on our primary endpoint to reduce the prevalence of PTS at two years. Our sample size calculations were performed for a two-tailed type I error rate of ≤5% and ≥80% power. Most publications provide conservative estimates of the prevalence of PTS as most studies under-report prevalence.The best estimate of prevalence was 25-50%, although several studies reported an even higher prevalence. Our first sample size calculation assumes a prevalence of 40% in control subjects and 20% in our exercise subjects. To show the reduction in prevalence we will need 164 subjects (82 in each group) in the randomized segment of the study.

Incorporating patients enrolled in the prior observational EFFORT protocol, plus anticipated attrition in the randomized trial (from loss to follow-up and deaths) we anticipate enrolling a total of 260 subjects in the entire EFFORT proposal.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

We will use exploratory data analyses (EDA) to review our data looking for extreme values which will be checked for transcription or other errors. Because our outcome measures will be measured multiple times (up to seven times, table I), we will use repeat measures ANOVA (SAS procedures PROC MIXED and PROC GLIMMIX) to compare outcome measures in the standard treatment and exercise groups. Both procedures allow for unbalanced and incomplete data, and will work when subjects are missing data at some time points. GLIMMIX allows for the selection of a link and response distribution and thus can be used to model counts (Poisson distribution with log link) or perform a logistic regression for binary outcomes (binomial distribution, logit link). We will use AICC (a variation of Akaike's information criterion) to select the covariance structure (unstructured, compound symmetry, first-order auto regressive) that best accounts for the serial autocorrelation of our repeated measures data. We will use random effects regression to compare the rate of change in our outcome variables in the standard treatment and exercise groups. Subject and time will be random effects (i.e. each subject will have his own intercept and slope). We will use regression analyses to compare the rates of change in key outcome variables in each of the Aims 11, 2 & 3 e.g. volume flow, systemic markers, venous hemodynamics, to the rate of change in the thrombus characteristics (volume, re-canalization score, elasticity).

We will use multiple imputation to produce estimates that account for missing values. Standard analyses assume that data are missing completely at random. Multiple imputation provides more efficient estimates for when data are missing completely at random, provides unbiased estimates (standard methods produce biased estimates in this situation), and provides estimates that are no worse than standard methods with non-ignorable missing data. Analysis results will be presented as point estimates ±95% confidence intervals. Analyses will follow an intent-to-treat paradigm and will be two-tailed. Prior to accepting the results of an analysis, we will check (e.g. examine residual plots) to make sure the data conform to the assumptions of the statistical method used to analyze the data.

Psychological/Behavioral/Educational Methods & Procedures

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

1 * Select all behavioral methods and procedures which apply to this study:

- [x] **Surveys/questionnaires**
- [ ] Key informant or semi-structured individual interviews
- [ ] Focus groups or semi-structured group discussions
- [x] **Audio or video recording/photographing**
- [ ] Educational tests or normal educational practices (education instructional strategies, techniques, curricula, or classroom management methods)
- [ ] Individual or group behavioral observations
- [ ] Psychosocial or behavioral interventions
- [ ] Neuropsychological or psychophysiological testing
- [ ] Deception
- [ ] Other psychosocial or behavioral procedures

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:
SF36
VEINS-QOL
Villalta

2 * Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
EFFORT Villalta.docx(0.01)	4/24/2014 12:42 PM	4/24/2014 12:42 PM
EFFORT VEINS-QOL.docx(0.01)	4/24/2014 12:42 PM	4/24/2014 12:42 PM
EFFORT SF-36.docx(0.01)	4/24/2014 12:36 PM	4/24/2014 12:36 PM

3 * What is the total length of time that each survey is expected to take?
5 minutes each

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)
○ Yes ● **No**

5 * Do any questions elicit information related to the potential for harm to self or others?
○ Yes ● **No**

5.1 If Yes, what procedures are in place to assure safety?

SF-36

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. 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?

	(Please circle one number on each line.)	Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please 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**
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

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

	(Please circle one number on each line.)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

VEINS-QOL

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

These questions are about your leg problem(s).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

VILLALTA

SCALE used to score each symptom and each clinical sign

None=0, Mild=1; Moderate=2; Severe=3

Symptoms

Pain	
Cramps	
Heaviness	
Paresthesia	
Pruritus	
Total	

Clinical Signs

Pretibial edema	
Skin induration	
Hyperpigmentation	
Redness	
Venous ectasia	
Pain on calf compression	
Venous ulcer (Y/N)	
Total	

VILLALTA Score:

Monitoring Plan Selection

1 * Type of data safety monitoring plan for the study:

- ○ Will use/defer to the external sponsor's Data Safety Monitoring Plan
- ○ Data Safety Monitoring by a Committee
- ● **Data Safety Monitoring by an Individual**
- ○ There is no data safety monitoring plan in place

Monitoring Plan - Individual

You indicated that the monitoring will be done by an Individual.

1 * Identify the individual who will be performing the safety monitoring:
Brajesh K Lal

2 * Describe this individual's role in relation to the protocol:
The major focus is on safety, particularly on expected and unexpected adverse events directly attributable to participation in the research; i.e. phlebitis due to an IV line insertion, fall on the treadmill, etc. All protocols will adhere to good clinical practice guidelines. In the review of the adverse events, the individual will review policies and procedures and make recommendation accordingly. If there is a serious unexpected adverse event that brings into question the safety of a procedure or of the protocol, the individual will temporarily suspend new enrollment into the protocol and work in concert with the VA Research Office and IRB to further evaluate the situation and determine if additional steps are necessary.

3 * What data will be reviewed?

- [x] **Adverse Events**
- [x] **Enrollment Numbers**
- [x] **Patient Charts/Clinical Summaries**
- [ ] Laboratory Tests
- [ ] Medical Compliance
- [x] **Procedure Reports**
- [ ] Raw Data
- [ ] Outcomes (Primary, Secondary)
- [ ] Preliminary Analyses
- [x] **Other**

3.1 If Other, specify:
QA audit reports, SOP, and consent forms when indicated

4 * What will be the frequency of the review?

- (●) **Annually**
- ( ) Bi-Annually
- ( ) Other

4.1 If Other, specify:

5 * Safety monitoring results will be reported to:

- [x] **IRB**
- [ ] GCRC
- [ ] Sponsor
- [x] **Other**

5.1 If Other, specify:
Self Monitoring.
The study is closed to enrollment.
All participants have completed the study and are now in data analysis only. Per GRECC please change the monitoring section to self-monitoring and remove GRECC ISMB.

Research-Related Costs

1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?

- ○ No
- ● **Yes**

1.1 If Yes, check all that apply:

- ☑ **Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)**
- ☐ Investigational or Study Device
- ☐ Investigational or Study Drug
- ☐ Investigational Procedure(s)

1.2 If No, who is responsible for payment?

2 * Who is responsible for the uncovered research-related costs?

- ☐ Participant
- ☐ Sponsor
- ☐ UM
- ☐ Other
- ☑ **There will be no uncovered research-related costs**

2.1 If Other, specify:

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

Compensation for Research-Related Injury

1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

◯ Yes ● **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date
There are no items to display		

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

◯ Yes ● **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date
There are no items to display		

Payment/Reimbursement to Participants

1 * Will participants receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research?

● **Yes** ○ No

Payment/Reimbursement Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research.

1 * Payment/reimbursement to participants will be for: (check all that apply)

- [ ] Travel
- [ ] Parking
- [ ] Meals
- [ ] Lodging
- [x] **Time and effort**
- [ ] Other

1.1 If Other, specify:

2 * What is the total dollar value of the payments/reimbursements over the duration of the study? ***Total payment(s) for participation in research of $600 or more in a calendar year is required to be reported on an IRS Form 1099.***
$240

3 * Describe the timing and distribution plan for the payment/reimbursement (schedule, means, etc.)?
Subjects will be paid according to the following schedule:
$20 after completing baseline testing
$30 after completing 1 month testing
$30 after completing 3 months testing
$40 after completing 6 months testing
$60 after completing 1 year testing
$60 after completing 2 year testing

4 * Method(s) of payment/reimbursement to be Used:

- [x] **Cash**
- [x] **Check**
- [ ] Money Order
- [ ] Gift Certificate/Gift Card
- [x] **Other**

4.1 If Other, specify:
Direct deposit

Audio or Video Recording/Photographs

You indicated that this study involves audio or video recording/photographing.

1

* Indicate the type of recording (check all that apply):

- [ ] Video
- [ ] Audio
- [x] **Still Photo**
- [ ] Other

1.1

If Other, specify:

2

* What is the purpose of the recording? (i.e., for therapeutic purposes, to establish treatment fidelity, or to establish reliability of assessments)

Due to COVID-19 concerns and restrictions, patients are provided the option of telehealth visits for their final follow-up visits (approved in modification 52). During a usual visit, visualization of the legs is documented. To better evaluate the legs during a telehealth visit, we would like to obtain still photographs of the affected lower extremities during the telehealth research visits to the study protocol.

3

* Could the recording be likely to cause discomfort in participants or cause harm if their confidentiality were breached?

- ○ Yes
- ● **No**

4

* How will individuals' identities be protected?

Photographs are taken only of the affected lower extremity. A unique identification code has already been assigned to each subject participating in this study. The photographs will be identified by the unique code.

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

1 * What type of samples will be involved in this study? (Check all that apply)

- [x] **Prospective (will be collected)**
- [ ] Existing (previously collected at the time of initial IRB submission)

2 * Will genetic analysis/testing be done on any of the samples?

● **Yes** ○ No

3 * Will this study involve banking of samples (storing for future research use)?

● **Yes** ○ No

4 * What is the purpose of the sample collection and/or analysis?

We will measure markers of inflammation, fibrinolysis, and angiogenesis in blood samples, as well as endothelial progenitor cells. We may measure new hormones, inflammatory proteins, and biomarkers as other technologies and findings are reported.

5 * Is there the possibility that cell lines will be developed with any of the samples?

○ Yes ● **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?

○ Yes ● **No**

6.1 If Yes, give name(s) and affiliation(s):

7 * Will the sample material be sold or given to any third parties?

○ Yes ● **No**

7.1 If Yes, give name(s) and address(es):

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

1 * What type of sample will be collected? (Check all that apply)

- [x] **Blood**
- [ ] Bone Marrow Aspirate/Biopsy
- [ ] Cerebrospinal Fluid
- [ ] Saliva
- [ ] Skin
- [ ] Sputum
- [ ] Stool
- [ ] Tissue
- [ ] Tumor
- [ ] Urine
- [ ] Other

1.1 If Other, specify:

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:
10 teaspoons of blood will be collected from each patient at baseline, 1 month, and 3 month visits.

3 * What type of samples will be collected? (Check all that apply)

- [x] **Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study**
- [ ] Samples obtained specifically for research purposes-additional taken during a clinical procedure
- [ ] Leftover samples that were obtained for clinical purposes (no additional research procedures required)
- [ ] Commercial (for profit) samples
- [ ] Other

3.1 If Other, specify:

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?
Unique identifier for the patient

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
Whatever samples have been collected will be anonymized and processed.

8 * Will the samples be destroyed after the study is over?
● **Yes** ○ No

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.

Genetics Research

You indicated that genetic analysis/testing is being done on the samples.

1 * How would you classify your genetic study? (choose all that apply)

- [ ] Gene Transfer
- [ ] Pedigree Study (to discover the pattern of inheritance of a disease and to catalog the range of symptoms)
- [ ] Positional cloning (to localize and identify specific genes)
- [x] **DNA diagnostic study (to develop techniques for determining the presence of specific DNA mutations or polymorphisms)**
- [ ] Other

1.1 If Other, specify:

2 * Discuss the potential for psychological, social, and/or physical harm that could result from participation in this research. In your discussion, consider the following aspects: risks to privacy, confidentiality, insurablity, employability, immigration status, paternity status, educational opportunities, or social stigma.

There is no potential for psychological, social, or physical harm; subjects and their physicians/insurance companies are blinded to their genotype, and the information is kept in a secure file by the investigators. We determine genotypes of the subjects and relate them responses to exercise. Reports about research done with samples will be included in study files and will be kept confidential to the best of our ability within state and federal laws. Participants will not be provided with the results of these tests as these measurements are for research purpose only and are not of proven clinical significance.

3 * Will subjects receive any information resulting from the genetic analysis?

○ Yes ● **No**

3.1 If Yes, describe the information that subjects will receive:
Please note: genetic analysis results should only be shared if the testing will be performed in a CLIA certified lab.

4 * Will participants be offered any type of genetic or educational counseling?

○ Yes ● **No**

4.1 If Yes, who will provide the education or counseling?

4.2 Under what conditions will education or counseling be provided?

5 * Is there the possibility that a family's pedigree will be presented or published?

○ Yes ● **No**

5.1 If Yes, describe how you will protect family members' confidentiality:

Sample Banking

You indicated that the study involves banking of samples (storing for future research use).

1 * Where will the sample(s) be banked? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number is was approved under.)
No samples will be banked for this study at the Baltimore VA Medical Center (VAMHCS).

2 * Does the banking institution have an approved policy for the distribution of samples?
● **Yes** ○ No

3 How long will the sample(s) be kept?
Samples will be stored until the final analysis is complete or unless the subject requests in writing to the PI that any remaining samples be destroyed.

4 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

5 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

6 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
All samples collected up to the time of participant withdrawal will be stored and analyzed unless the subject requests in writing that any remaining samples be destroyed.

7 * If the participant withdraws, explain how the data obtained from their sample(s) will be handled (e.g., will it be deleted?) ***(Please note that data for FDA regulated research cannot be deleted):***
All data collected until the time of withdrawal of the participant will be stored indefinitely unless the subject requests in writing that any remaining samples be destroyed.

Data Collection/Record Review

You indicated on the "Type of Research" page that your study involves data collection or record review (i.e., chart review, not self-report).

1 * What type of data will be collected/analyzed in this study? (Check all that apply)

- [ ] Retrospective/Secondary Analysis (data has already been collected at the time of initial IRB submission)
- [x] **Prospective (data is not yet in existence and/or collected)**

2 * Will this study involve adding data to a registry or database for future use?

○ Yes ● **No**

3 * Will the data be released to anyone not listed as an investigator on the protocol?

○ Yes ● **No**

3.1 If Yes, give name(s) & affiliation(s):

Prospective Data

You indicated that the study involves the collection of prospective data.

1 * Where is the data being collected from? (Check all that apply)

- [x] **Medical records**
- [x] **Medical images**
- [ ] Commercial (for profit) entity
- [ ] Publicly available records
- [ ] Schools
- [ ] Other

1.1 If Other, please specify:

2 * What data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.

Name, initials, date of birth, Social Security number, medical record number, demographic information, dates for tests performed

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date

There are no items to display

Eligibility

1 * Do you have an existing Eligibility checklist(s) for this study?

◯ Yes ● **No**

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
There are no items to display		

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Acute Lower Extremity DVT
View	2	Documented by ultrasound, CT/MR venogram, or conventional venogram
View	3	Diagnosis of DVT within the last 4 weeks.
View	4	Age ≥18 years

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Peripheral arterial disease (disabling claudication, rest pain, tissue loss) with ABI<0.5
View	2	Immediate need for thrombolysis/thrombectomy
View	3	DVT involving the IVC
View	4	Contraindication to anticoagulation
View	5	Contraindications to exercise training
View	6	Life expectancy <2 years
View	7	Pregnancy
View	8	Hemodynamically significant PE
View	9	Other medical condition precluding patient participation in this study per medical judgement of study team.

Recruitment

1 * Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):
Subjects will be recruited from the UMMS Vascular Clinic and the UMMS and VAMHCS Vascular Labs. The UMMS Vascular clinic and the UMMS and VA Vascular Labs have a substantial referral base and are currently diagnosing approximately 500 such patients per year who could be enrolled in the study. Patients will be identified on presenting to the clinic leg pain and/or swelling. The Vascular Clinic and Labs receive referrals from multiple sub-specialties such as the Anti-coagulation Clinic and primary care physicians.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter "N/A"):
The study purpose, procedures, risks, and benefits will be explained to the patient. Patients who wish to speak with their own physician will be encouraged to do so. They will be informed that they are at liberty to refuse participation or to withdraw at any time. Written informed consent will be obtained from all patients enrolled in the study.

3 * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)

- [x] **PI**
- [x] **Study Staff**
- [ ] Third Party

Advertising

1 * Will you be using advertisements to recruit potential participants?

◯ Yes ● **No**

ID: VIEW4E0BCCF811000
Name: v2_Advertising

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1 * Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:

3D Ultrasound for thrombus volume, vein wall elasticity, and venous flow. The non-invasive test will be performed while lying down with minimal discomfort using a clinical ultrasound machine.

Questionnaires for Quality of Life (VEINS-QOL & SF-36), post thrombotic syndrome severity (Villalta score). There are no significant risks to the subjects, except for potential anxiety while answering questions regarding their symptoms and signs. Every effort will be made to ensure patient comfort during testing.

Blood draw (10 tea spoons) for markers of fibrinolysis, inflammation and angiogenesis. This will be accompanied by minor discomfort such as pain, bruising and bleeding. Phlebotomy will be explained carefully and will be conducted according to clinical standard of care using standard aseptic technique.

Supervised upper and lower body exercise and exercise testing. The risks for exercise testing and training are minimal, but occasionally include fainting, dizziness, chest pain, irregular heartbeats or sudden death, and complications related to stress and strain of a muscle, twisted ankles, and/or falls. The American Heart Association estimates the risk of a heart attack to be very low at about 1 in 60,000 hours of exercise. In addition, participants will be monitored by trained personnel during testing and exercise training to limit these risks. Care will be taken to have a clinician available during all exercise testing. This will ensure that no clinical symptoms or signs of PE will be missed. In addition, patients will be counseled on the classic presentation for a PE and they will be encouraged to inform us if they feel any symptoms during exercise. The risk for pulmonary embolism is greatest immediately after DVT (until the clot becomes stabilized). During this time period we will not have our subjects exercise their lower extremities. We have our subjects exercise only their upper body, which we have shown increases venous flow to both the upper and lower extremity.

NMES. Risks associated with NMES include skin irritation and muscle soreness. The risk of skin irritation will be minimized by observing the participant during the initial training sessions, ensuring that electrodes are properly moistened and applied, and by monitoring the skin under the electrodes after stimulation. If skin irritation is present, study staff will advise the participant on how to care for the irritation under Dr. Lal's supervision. The risk of muscle soreness, either acute or delayed, will be minimized by phasing-in the time and intensity of stimulation, starting at a low level and gradually increasing as tolerated. If soreness does occur, participants will be informed on how to minimize and treat the soreness.

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the potential direct benefit(s) to participants:
There may be no guaranteed direct benefit to the patient in the study, although many patients involved in studies of this type feel their care is improved by the frequent follow-up and examinations as part of the study. However, the study could identify that exercise enhances thrombus resolution and that it prevents PTS. We anticipate that knowledge gained from this study will provide additional treatment options for patients at risk of PTS to enhance their rate and completeness of recovery. Therefore, this study could potentially provide highly significant information by subjecting patients to the minimal risks of questionnaires, non-invasive testing, and exercise.

2 * Describe the importance of the knowledge expected to result from the study:
This project is intended to provide crucial knowledge about the contribution of enhanced venous flow to accelerating thrombus resolution in the deep venous system. This could in turn result in reduced incidence and severity of PTS.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:
There are minimal risks associated with this research protocol. There are no invasive interventions planned. With that in mind, all knowledge gained by the study will be extremely useful and obtained at minimal risk to the patients.

4 * Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.
Participation is voluntary and the alternative is to not participate.

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 * Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:
The person in charge of the research study can remove the participant from the research study without their approval. A possible reason for removal is failure to follow instructions of the research staff or the signed consent form. In addition, if the person in charge decides that the research study is no longer in the participant's best interest, the participant may be removed. The sponsor can also end the research study early. The study doctor will tell the participant about his/her decision and give them the chance to ask questions if this were to happen.

2 * Describe procedures for orderly termination:
Participants will notify the PI or staff if they wish to withdraw from the study. If the PI finds reasons to exclude or withdraw a study participant, that participant will be contacted and informed as to why they are being withdrawn.

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:
Data and samples collected prior to withdrawal (or from continued data collection in the case of partial withdrawal) will be kept in a secured database. Samples are coded and the key to the code is kept separately in a secured location by the investigator.

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 * Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***
All subjects will have privacy i.e. the right to control access to themselves. Study interviews will be held by a member of the study team only in a private setting.

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:
In a private setting. Consent will be obtained by the PI or his team in writing in a closed office, exam room, or conference room.

3 * Describe potential environmental stressors that may be associated with the research:
We do not identify any potential stressors with this research.

4 * Will this study have a site based in the European Union?
○ Yes ● **No**

5 * Will the study have planned recruitment or data collection from participants while they are located in the European Union?
○ Yes ● **No**

Confidentiality of Data

1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

- (●) **Yes**
- ( ) No, the data will be stored de-identified/anonymous (stripped of all identifiers, no way to identify individual participants)

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)

In the vascular research office on the 6th floor of the Baltimore VA Hospital in a locked file cabinet behind two locked doors. All electronic data will be stored on the VA network behind the firewall in the VA Vascular Research Office.

3 * How will such data be secured?

Behind two locked doors. All electronic data will be stored behind the VA Firewall and only the research team members working on the study will have access to the data.

In response to the COVID-19 pandemic, participants will be given the option to participate in telehealth follow-up visits via a VA approved communication platform (Apple FaceTime, Facebook Messenger video chat, Google Hangouts video, Skype, or WhatsApp). Participant data will be protected to the greatest extent possible while using this alternative technology including enabling all available encryption and privacy modes when using such applications. PHI and PII shall not be recorded or stored using audio or video communication technology.

4 * Who will have access to research data?

Principal Investigator, sub investigators, and the research team.
Research data will be stored and destroyed in accordance with RCS10-1.
Removal of access to research study data will be promptly accomplished for study personnel when they are no longer part of the study and/or research team.
Research information will not be removed from protected VA environment.

5 * Will study data or test results be recorded in the participant's medical records?

( ) Yes (●) **No**

6 * Will any data be destroyed? ***(Please note that data for FDA regulated research cannot be deleted however, VA data must be destroyed according to the VHA Records Control Schedule (RCS) 10-1)***

( ) Yes (●) **No**

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

7 Do you plan to obtain a Certificate of Confidentiality?

( ) Yes (●) **No**

7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name	Created	Modified Date

There are no items to display

8 * Discuss any other potential confidentiality issues related to this study:

There is a potential loss of confidentiality as a result of participation in the study. Personal health information obtained by the investigators as part of this research protocol will be shared by individuals mentioned in the HIPAA document. It is possible that personal information could inadvertently be shared by others. All records of the VA participants will be flagged in the VA CPRS system to indicate they are participating in the study. In the case of an incident at the VA the VAMHCS PO and ISO will be contacted.