# Exercise Training for the Treatment of the Post-Thrombotic Syndrome: The EXPO Pilot Trial

**Abbreviations used in this proposal:** ECS (elastic compression stockings), EST (exercise stress test), DVT (deep venous thrombosis), PE (pulmonary embolism), PTS (post-thrombotic syndrome), QOL (quality of life), VTE (venous thromboembolism).

## 1. THE NEED FOR A TRIAL

### 1.1 What is the problem to be addressed?

The proposed randomized controlled two-centre pilot trial will assess the feasibility, tolerability and effect size of a program of exercise training to treat the post-thrombotic syndrome (PTS). Results of this pilot trial will be used to plan a larger, adequately powered, multicenter randomized trial of exercise training to treat PTS.

#### 1.1.1. Overview of the post-thrombotic syndrome

**Relationship between deep venous thrombosis and the post-thrombotic syndrome**

Deep venous thrombosis (DVT) is a common clinical problem that affects more than 250,000 people in the U.S. and 25,000 people in Canada each year [1]. When DVT is diagnosed, prompt initiation of anticoagulant treatment is highly effective at reducing the immediate risk of potentially fatal pulmonary embolism (PE) as well as the longer term risk of recurrent episodes of DVT and PE [2]. However, despite receiving appropriate anticoagulant treatment, up to one-half of DVT patients will develop a chronic, life-long complication termed the post-thrombotic syndrome (PTS) (also known as the post-phlebitic syndrome).

Patients with PTS experience significant pain, heaviness, swelling and cramping in the lower extremity. Symptoms are typically aggravated by standing or walking (known as "venous claudication") and are lessened by leg elevation or lying down. Clinical signs of PTS include edema, venous ectasia, brown hyperpigmentation, eczema and varicose collateral veins. In severe cases, lipodermatosclerosis (skin thickening and contraction) and painful venous ulcers may occur [3,4].

Our recent systematic review of the occurrence of PTS in prospectively followed DVT patients showed that the incidence of any PTS was 46%, of severe PTS (including venous ulcers) was 15% [5], and that in most cases, the condition developed within 1-2 years of the acute DVT. Indeed, PTS is the most common complication of DVT.

**Cost and burden of PTS**

PTS is not merely a cosmetic or "nuisance" problem. Rather, PTS is costly and burdensome to patients and society, both in terms of dollars spent and effect on quality of life and productivity [6]. A U.S. study estimated that the annual direct cost of PTS is at least $200 million dollars [7]. In a recent Canadian study, the annual cost of venous ulcer care in Ottawa alone was greater than $1,000,000 and a large number of these cases are secondary to previous DVT [8]. Our own research has shown that patients with PTS have significantly poorer quality of life than DVT patients without PTS [9,10], that quality of life is lower than in patients with other forms of chronic venous disease [11] and that impairment in quality of life is, on average, worse than in patients with osteoarthritis or chronic lung disease [9,12].

**Pathophysiology of PTS**

When DVT is diagnosed, standard anticoagulant treatment prevents thrombus extension and embolization to the pulmonary arteries, but does not directly lyse the acute thrombus. Follow-up studies of patients with DVT who were treated with anticoagulants have shown that in most cases, only partial clearance of thrombus occurs and return of normal physiological function of the vein is rare[13-15]. Even in patients who do achieve clot lysis, permanent damage to venous valves occurs frequently, conceivably via thrombus-induced activation of inflammation [16,17] or scarring associated with acute

and resolving thrombosis, leading to valve incompetence (reflux). Indeed, the use of thrombolysis to treat DVT, while achieving high rates of clot lysis, has not been definitively shown to improve venous hemodynamics or reduce the risk of PTS, compared with standard anticoagulation [18].

Based on the above and on results of venous hemodynamic studies in patients with PTS [19-22], it is likely that the pathophysiology of PTS involves the interplay of two processes: (1) damage to delicate venous valves by the thrombus itself or by associated inflammatory mediators, which causes valvular reflux; and (2) residual venous obstruction due to incomplete thrombus clearance, which leads to impaired venous return. Both processes lead to increased venous pressure (venous hypertension), which results in reduced calf muscle perfusion, increased tissue permeability and the associated clinical manifestations of PTS (e.g. pain, effort intolerance, swelling).

**Currently available treatments for PTS**

In contrast to the gains achieved in treating acute DVT [2], there are very few treatment options for PTS. Clinicians often prescribe physical compression methods to counteract increased venous pressure. However, a recent Cochrane review [23] concluded that (1) there is no evidence to support the use of elastic compression stockings (ECS) to treat PTS, and (2) while intermittent pneumatic compression units may be of benefit in patients with severe edema, they are cumbersome, expensive and data are inadequate to draw conclusions about their long term effects. Regarding medications to treat PTS, there is limited evidence that "venoactive" agents such as aescin or rutosides may reduce symptoms of chronic venous insufficiency [24,25] and in one study these improved PTS symptoms in the short-term [26]. However, the long-term benefit and safety of these medications have not been evaluated in large controlled trials. Surgical treatments for PTS such as venous valve repair or venous bypass have been evaluated primarily in small patient series at single, specialized centers and appear to be of limited value [27,28]. Finally, post-thrombotic venous ulcers are generally treated with compression therapy, leg elevation and topical dressings but are often refractory to therapy and tend to recur [4,29].

In summary, effective, evidence-based treatments for PTS are lacking, which has long been a source of difficulty and frustration for patients with PTS. New approaches to the treatment of PTS are greatly needed.

### 1.1.2 What is the rationale for a study of exercise training to treat PTS?

**1.1.2.1 Exercise training is effective for arterial claudication via mechanisms that could be relevant for PTS**

Akin to patients with PTS, patients with arterial claudication (i.e. due to peripheral arterial disease) experience walking-induced leg pain that primarily affects the calves. Pain persists or worsens with continued walking and is relieved by rest. Because of impaired walking ability, patients have difficulty carrying out daily activities and become deconditioned from lack of exercise [30].

Exercise training is an effective treatment for arterial claudication. A meta-analysis that examined both nonrandomized and randomized trials showed that exercise training improved pain-free walking time in patients with claudication by an average of 180% and maximal walking time by 120% [31]. The greatest improvements occurred when each exercise session lasted >30 minutes, was continued until near-maximal pain was reached, took place at least 3 times per week and was continued for a program duration of 6 months or longer. A recent Cochrane meta-analysis reviewed only high quality randomized trials of exercise to treat claudication [32]. All exercise interventions involved a regimen of training or walking at least twice weekly that ranged from 3-12 months in length and included some element of supervision. Comparators included placebo tablets, drug therapy (e.g. antiplatelets, pentoxifylline) or surgical interventions (angioplasty, bypass). Results from 10 studies (total of 250 patients) showed that overall, exercise consistently and significantly improved maximal walking time by an average of 150% (range 74-230%) compared with all control groups except bypass surgery, where improvements were of similar magnitude to exercise.

In terms of mechanism of action, exercise does not consistently improve ankle-brachial index or promote growth of major collateral vessels, suggesting that the benefits of exercise are not due to improved blood flow through large vessels [30]. Instead, the benefit of exercise is likely to be the result of a combination of other mechanisms. First, there may be an increase in capillary density and changes in endothelial function that improve the matching of blood supply to metabolic demands; both of these adaptations are expected to increase oxygen delivery and excretion of carbon dioxide and other metabolites. Second, there may be changes in muscle metabolism that result in improved oxidative capacity and oxygen extraction from perfusing blood. Third, exercise may promote neuromuscular learning and improve walking biometrics, both of which are expected to result in greater exercise efficiency (i.e., conversion of metabolic activity into mechanical work) [30,33,34].

It is plausible that these mechanisms could also be relevant to patients with PTS. Histological studies of muscle tissue indicate that venous hypertension causes hypoxic damage to contractile fibers and mitochondria of calf muscle with resultant atrophy and muscle fiber necrosis [35,36], and hemodynamic studies show that venous hypertension reduces calf muscle perfusion (difference between arterial and venous pressures) [37]. Such changes would be expected to lead to muscle weakness and reduced endurance. Indeed, hemodynamic and clinical studies have demonstrated that patients with PTS have impaired calf pump function and increased calf muscle fatigability, which manifests as effort intolerance [38-40]. Aerobic training, by increasing oxygen delivery to muscle fibers and improving metabolism and oxidative capacity of muscle, combined with strength training targeted at strengthening the calf muscle pump and flexibility training to improve leg mobility could lead to reduced effort intolerance, pain due to build-up of metabolic products (e.g. lactate) during exercise and leg swelling due to improved venous return and thereby achieve overall improvement of PTS.

**1.1.2.2 Studies of exercise in venous disease support a trial of exercise training to treat PTS**

The effectiveness of exercise training to treat PTS has not previously been studied. However, a few studies, discussed below, have addressed some aspects of exercise in patients with acute DVT or PTS.

Our group performed 2 studies as preparatory work for this proposal (publications included in Appendix). First, in a cohort study, we evaluated whether exercise increased the severity of venous symptoms in patients with previous DVT [40]. We recruited 41 subjects (mean age 50, M=F) with previous unilateral DVT, 19 of whom had PTS (2 severe), from the Thrombosis Clinic at the Jewish General Hospital in Montreal. Subjects underwent a single treadmill exercise session (walking or running at a speed that caused mild tachypnea and sweating, up to a maximum of 30 minutes). Venous symptoms, calf muscle fatigability, flexibility, and leg volume were measured in the affected leg before and after treadmill exercise and compared in subjects with and without PTS. We found that subjects with PTS had more calf muscle fatigability and poorer calf flexibility at baseline than subjects without PTS. Exercise led to a significant improvement in calf flexibility in subjects with PTS (gastrocnemius + 4.5°; soleus + 5.7°) and did not worsen venous symptoms. Based on these results, an editorial accompanying our article called for a trial of exercise training to treat PTS [41]. Second, to address the longer term effects of exercise after DVT, we performed a multicenter prospective cohort study to evaluate whether increased physical activity 1 month after DVT led to worsening of venous symptoms and signs within the subsequent 3 months [42]. Of 301 patients (mean age 56; M=F) followed for 4 months, 25% were inactive and 25% were only mildly active before their DVT. Multivariate analyses adjusted for disease severity at one month suggested that higher physical activity levels at 1 month might be protective against worsening of venous symptoms and signs over the subsequent 3 months. Compared with those who were inactive at 1 month, the adjusted OR for worsening of symptoms/signs was 0.93 (95% confidence interval [CI] 0.47, 1.87) for mild-to-moderately active persons and 0.52 (95% CI 0.24, 1.15) for highly active persons. Hence, higher level of physical activity at 1 month post-DVT does not appear to worsen (and may improve) venous symptoms/signs over the subsequent 3 months.

To our knowledge, only 2 other studies that relate to exercise and venous disease have been published. The first study addressed the role of early ambulation after diagnosis of acute DVT. Partsch found that patients with proximal DVT who were "up and about" and wore ECS immediately after diagnosis had faster resolution of acute symptoms, no increased risk of PE and a lower frequency of PTS at 2 years than patients who were initially assigned 8 days of bedrest followed by ECS use [43,44]. Of greater relevance to this proposal, the second study, by Padberg, was a single center randomized trial of exercise training in patients with severe chronic venous insufficiency of diverse etiology [45]. Thirty subjects were randomized to (1) 3 months of supervised exercise therapy designed to strengthen calf musculature and enhance joint mobility followed by 3 months of unsupervised therapy, or (2) a "wait-list" control. All were prescribed ECS. After 6 months of exercise, physiological indicators of calf pump function and calf muscle strength improved in the exercise group but not in the control group. There no apparent differences in quality of life or venous symptom scores between groups however the trial was underpowered for these outcomes. The authors reported that of 77 patients screened, 30 were eligible and willing to participate, compliance (% of sessions attended and mean number of exercise days) was good during both the supervised and unsupervised phases and no adverse events occurred. This trial provides helpful information regarding the feasibility, tolerability and safety of a 6 month exercise program in patients with chronic venous insufficiency. However, as patients were older than average DVT patients (70 vs. ~50 years), as no women were included and as only half of patients had previous DVT, the results are not directly generalizable to patients with PTS.

Extrapolating from the above, we reason that a 6 month exercise training program for patients with PTS is unlikely to be harmful, is likely to be feasible, may be of benefit and is worthy of study. However, a pilot study is required to support this before proceeding to a large, multicenter trial.

### 1.2 What are the principal research questions to be addressed?

In our proposed pilot trial, we will randomize patients with PTS to 1) a 6-month exercise training program designed to improve leg strength, leg endurance, leg flexibility and general cardiovascular fitness (Active Training) or 2) an Attention Control group.

- Our feasibility objectives are to assess levels of patient eligibility, consent, adherence and retention.
- Our scientific objectives are to obtain estimates of effect size associated with Active Training, by describing within-subject change over 6 months in quality of life (QOL), severity of PTS, calf strength, calf flexibility and exercise capacity (time-on-treadmill) in the Active Training and Attention Control groups.
- Our results will inform the design of a large, multicenter trial of exercise training to treat PTS.

### 1.3 Why is a trial needed now?

**DVT is a common condition and PTS is a frequent consequence of DVT**: The annual incidence of VTE (DVT and PE combined), estimated at 1-2 per 1000 persons per year, has not decreased over the last few decades [1,46,47]. PTS is a direct, frequent consequence of DVT that is costly and burdensome. As discussed in Section 1.1.1, no effective therapies for this condition are currently available.

**Expert opinion supports the need for effective, evidence-based treatments for PTS**: Government, expert consensus and patient advocacy bodies have expressed that there is an important need to find effective therapies for PTS. In 2005, the **National Heart, Lung, and Blood Institute of the NIH** issued a Request for Applications to support research on venous biology and post-thrombotic response of the vein wall, with the goal of "accelerating preclinical studies, developing better management principles of PTS, contributing to the translation of basic research to clinical studies and ultimately leading to innovative approaches to prevention and treatment of PTS". The lack of effective treatment

for PTS was also highlighted in the most recent (2004) version of the **American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy**, an international consensus group that issues regularly updated, evidence-based management guidelines widely considered to represent the standard of care for thrombotic disorders. The chapter on Treatment of VTE concluded that "treatment of PTS has only been evaluated in small or methodologically flawed trials" [2]. Of the close to 100 treatment recommendations issued in this chapter, only 3 pertained to PTS, and all received poor grades for quality of the underlying evidence. Dr. S. Moll, Scientific Chairman of the **North American Alliance on Thrombosis and Thrombophilia** (www.nattinfo.org), a USA-wide, community-based, volunteer health organization committed to fostering research, education, support, and advocacy for those at risk of or affected by blood clots, considers our proposed trial to be of very high relevance to the estimated 340,000 patients in the U.S. who suffer from PTS and provides his full endorsement on behalf of NATT (see **Letter of Support, Appendix**).

**Previous work provides foundation for a trial of exercise to treat PTS**: As detailed in section 1.1.2.2, our proposed trial builds directly on previous work performed by our group [40,42,48,49].

**Conclusions**

PTS is a common and burdensome condition for which there is no proven effective treatment. Exercise training is effective for the treatment of arterial insufficiency via mechanisms that may also be relevant to PTS. Pilot work completed by our group as well as a small trial in patients with chronic venous insufficiency suggest that exercise training, which is safe, inexpensive and has numerous health benefits [50] will be feasible, well tolerated and could be effective for the treatment of PTS.

Our proposed EXPO Pilot Trial is innovative because: (1) the potential benefit of exercise training for the treatment of PTS, while plausible, has not previously been studied; (2) there have been virtually no previous randomized trials of PTS treatment; and (3) trial outcomes include both patient-based (i.e. QOL) and physiological measures.

### 1.4 Give references to any relevant systematic reviews

We searched for systematic reviews, individual published studies and registered clinical trials (actively recruiting or closed to recruitment) pertaining to exercise as an intervention to treat PTS. No relevant "hits" were found. Therefore, our proposed trial will be the first trial of exercise training specifically for the treatment of PTS. **Table 1 (pg. 12o) shows details of our search strategy and results.**

### 1.5 How will the results of this trial be used?

Data on feasibility and effect size obtained in the EXPO Pilot Trial will be used to decide whether to proceed to apply for funding for a larger, broadly generalizable multicenter trial of exercise to treat PTS, and will directly inform the design of this larger trial. For the larger trial, we aim to develop and study the effectiveness of an exercise regimen that could be practically implemented at multiple study centers in a broad range of PTS patients using endpoints that are clinically relevant and readily measurable. If the benefits of exercise training are confirmed in the larger trial, this evidence will be incorporated into international consensus guidelines of VTE management, will be disseminated to health organizations involved with the care of DVT patients (e.g. National Alliance for Thrombosis and Thrombophilia, Thrombosis Interest Group of Canada, Quebec Vascular Sciences Society) and will be directly translatable to clinical practice. Hence, our study has the potential to have a direct, positive impact on the health of patients with PTS and could contribute important new knowledge to a field of research that has previously received very little attention.

### 1.6 Describe any risks to the safety of participants involved in the trial.

The safety risks to participants are anticipated to be small. In a review of trials of exercise training to treat intermittent claudication, no cardiac events or deaths were reported [32]. In a study of a

6-month exercise program for older patients with chronic venous insufficiency, there were no adverse events attributable to exercise [45]. However, to enhance safety, prior to enrollment in the EXPO Trial, a physician-supervised, maximal exercise treadmill test (EST) will be performed in all subjects. If abnormalities (e.g. ECG changes indicating ischemia or arrhythmia, hypotension or severe hypertension) are detected, appropriate medical management will be arranged and the subject will be excluded from participation. As subjects will be recruited at least 6 months after the diagnosis of DVT, there is no expected risk of exercise-induced clot embolization. With any exercise program, there is some risk of muscle stiffness or pain that typically resolves with rest and with habituation to the program. This risk will be minimized by the use of experienced exercise physiologists at each site who will ensure that exercises are performed with proper technique. All potential safety risks will be described in the Trial Consent Form. Informed consent will be obtained from all patients prior to participation in the study. Potential adverse events (e.g. exacerbation of leg symptoms, recurrent DVT, PE) will be reported during study follow-up. In addition, safety will be carefully tracked on an ongoing basis by a Safety Monitoring Committee. Confidentially will be maintained and subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

## 2. THE PROPOSED TRIAL

### 2.1 What is the proposed trial design?

The study design is that of a randomized, allocation concealed, controlled, two center (Montreal and Ottawa) pilot trial evaluating the feasibility and effect of a 6 month exercise training program to treat PTS (**Figure 1: Study Schema, pg 12n**). Study physicians and assessors performing measurements, but not patients and exercise physiologists, will be blind to treatment allocation group.

Justification of overall trial design:We considered but rejected 2 alternate study designs. A randomized crossover design, by eliminating variability in treatment response due to inter-subject differences, would have increased efficiency. However, we were concerned about probable carry-over effects of the exercise intervention. A study of two parallel cohorts (Active Training and Attention Control cohorts) could have led to a simpler, less costly study. However, as we intend to use the results of our study to design a larger multicenter RCT, a pilot RCT is essential to help identify feasibility problems.

### 2.2 What are the planned trial interventions?

#### 2.2.1. EXPERIMENTAL INTERVENTION

**Active Training (AT):** 6-month exercise program designed to improve leg strength, leg flexibility and cardiovascular fitness, as outlined below. Stress testing, exercise prescription and exercise supervision will be conducted as described below in Montreal through the Cardiovascular Health Improvement Program (CHIP) and in Ottawa through the Prevention and Rehabilitation Centre of the University of Ottawa Heart Institute.

***General Principles of Active Training intervention:*** The Active Training intervention consists of strengthening, stretching and aerobic components. As the principal muscles affected by PTS are the lower limb muscles, we will target our training program to improve range of motion and endurance of the principal knee extensors (quadriceps), knee flexors/hip extensors (hamstrings) and ankle plantarflexors (gastrocnemius/soleus). To maximize generalizability and reduce expense, we have chosen to focus on exercises that do not require use of equipment. Because some of our patients may be unfamiliar with exercise programs, we feel that one-on-one supervision by an exercise physiologist with more frequent sessions at the beginning of the study is appropriate and justified in order to maximize motivation and to ensure that subjects train at their prescribed level of exercise and learn the correct technique to avoid injury. ***Training schedule and procedures:*** During the 26-week training intervention, patients will meet 15 times with the same exercise physiologist (3 face-to-face sessions per week for each of the first 2 weeks, 2 face-to-face sessions per week for the third week, one session per week during week 4, and then one session per month for the rest of the 6-month program). The

first 3 visits will be approximately 60 minutes, with 45 minute follow-ups scheduled for all other visits. The initial session will include a brief overview of the benefits of exercise, review of the pre-randomization EST results, an individualized exercise prescription, and a supervised exercise training session. Principles of warm-up and cool-down along with basic stretching exercises and general exercise precautions will also be reviewed to minimize the risk of injury. The exercise prescription will be individualized and will follow guidelines from the American College of Sports Medicine for developing and maintaining cardiorespiratory fitness [51]. These guidelines suggest that individuals perform 60-120 minutes/week of aerobic exercise within their target heart rate zone (60-85% of maximal heart rate). Subjects randomized to Active Training will be provided with a digital heart rate monitor (POLAR FS1 model) to aid with exercise prescription and to enable subjects to verify that they are training at the prescribed intensity level. **Strength and flexibility exercises and further detail on the Active Training program are presented in Table 2, pgs. 12p-r.** Follow-up sessions with the exercise physiologist will consist of providing guidance and support to the subjects, solving any difficulties, and gradually increasing the intensity of the exercise. If the exercise physiologist judges that the subject is comfortable with the exercises and understands the principles of how to modify the program so that they continue to achieve a training effect, some of the face-to-face sessions may be replaced with telephone interviews. Such changes will be carefully documented.

#### 2.2.2. CONTROL INTERVENTION

**Attention Control (AC):** 6-month program consisting of (1) standardized 1-hour education session on PTS (what PTS is, why patients get it, how to manage it; exercise will be kept "neutral"-i.e. not specifically addressed) given by a trained thrombosis nurse-educator not involved with the assessment of study outcomes, and (2) monthly phone contacts by the same thrombosis nurse to "check in" with the patient, ask about their PTS and provide support.

The goal of the attention control (vs. no control) is to provide a control intervention to simulate the contact subjects in the exercise group will receive. Attention controls have been used successfully in a number of trials of long term exercise programs [52-55]. We considered but rejected alternate types of controls: Sham exercise control - sham exercise (e.g. upper body-only exercise, or very light training) could result in treatment contamination in itself or if it led subjects to also take up other forms of exercise. In addition, we believe that sham exercise is not likely to be perceived by subjects as a convincing intervention. Wait-list control - as this trial is a pilot study that will not provide definitive results, a wait-list control (patients randomized to no exercise would be offered the exercise intervention at study end, if it is shown to be effective) is not appropriate. Active control - as there is no proven effective therapy for PTS, an active control is not indicated.

Note: The use of ECS will not be mandatory during the trial as these are not proven to be effective for the treatment of PTS [23] and a study performed by our group showed that wearing ECS during exercise appears to have neither harmful nor beneficial effects [48]. However, ECS use (and reasons for use) will be tracked and examined as a covariate in the analysis.

### 2.3 What are the proposed practical arrangements for allocating participants to trial groups?

Eligible, consenting subjects will be individually randomized via a web-based program using permuted blocks of 4 and 6 (size of blocks randomly ordered) to Active Training or Attention Control (1:1 allocation ratio). Stratification by study centre (Montreal & Ottawa) will be performed.

### 2.4 What are the proposed methods for protecting against sources of bias?

Because of the nature of the exercise intervention, it is not possible to blind patients to treatment group. However, several strategies will be used to protect against bias. Randomization with allocation concealment will be used to assign treatment group. Consecutive patients who are eligible and provide consent will be enrolled using strict inclusion and exclusion criteria. We will use an

attention control (a control group that is not merely left untreated and followed, but receives an "attention" intervention in the form of education and regular contact) to reduce the likelihood that any observed changes in the Active Training group could be due to a Hawthorne effect. To reduce measurement bias, (1) outcome assessors administering questionnaires or performing objective assessments (e.g. EST, flexibility and strength testing) will be blinded to treatment assignment (subject randomization and delivery of the attention control intervention will be not be performed by research staff performing outcome assessments), and (2) validated measures, instruments and techniques will be used to assess all outcomes. To reduce the risk of treatment contamination, patients in the Attention Control group will be asked to not change their usual level of physical activity during study follow-up (this will be assessed by administering the IPAQ physical activity questionnaire [56] at study visits: see section 2.13) and crossover between treatment groups will not be permitted. Use of potentially effective co-interventions (e.g. ECS) will be recorded. Introduction of conventional or naturopathic medication for treatment of PTS will be discouraged during the 6 months while patients are in the study, and their use will be monitored. Subjects who decide to discontinue the trial will be asked to return for the final assessment and will be included in the intent to treat analysis.

### 2.5 What are the planned inclusion and exclusion criteria?

Subjects will be recruited from Thrombosis Clinics in Ottawa and Montreal.

**Inclusion criteria**

1. Age 18-75.
2. Previous unilateral DVT diagnosed using standardized ultrasound or venographic criteria [57,58].
3. PTS in same leg as previous DVT (Villalta PTS scale [59] score >4). **See Appendix for copy of Villalta scale and justification of its use to diagnose PTS.**

***Rationale for inclusion criteria***: Patients with prior bilateral DVT or who have bilateral PTS will not be included so as to permit within-patient comparisons of affected and unaffected leg for the physiological measures. Limiting enrollment to sedentary patients who may be more likely to derive benefit from exercise was considered. We also considered limiting enrollment to patients with moderate or severe PTS only. However, at this preliminary stage, we did not feel that there was compelling data to support restriction of inclusion on these factors. The impact of baseline habitual physical activity and PTS severity on effect size will be examined in the analysis.

**Exclusion criteria**

1. Acute DVT within previous 6 months (to ensure that patient has PTS rather than slow-to-resolve acute DVT symptoms [60] and because of a small theoretical risk of exercise-induced dislodgement of fresh thrombus).
2. Contraindications to exercise training, e.g. arthritis of lower extremities, angina, symptomatic chronic obstructive lung disease, congestive heart failure, severe claudication, poor balance.
3. Expected lifespan < 6 months or general medical condition that would make study infeasible, e.g. advanced cancer or cardiopulmonary disease.
4. Pregnancy or lactation.
5. Open venous leg ulcer.
6. Not conversant in either English or French.
7. Geographic inaccessibility which precludes participation.
8. Unwilling or unable to provide signed informed consent.
9. Screening (i.e. pre-randomization) Exercise Stress Test (Bruce ramp protocol [61]) demonstrating uncontrolled hypertension, ischemia, or arrhythmia (such patients will be referred for appropriate medical evaluation)

### 2.6 What is the proposed duration of treatment?

We plan a 6 month program of exercise training. This duration has been shown to be feasible and effective for the treatment of arterial claudication [30-32] and chronic venous insufficiency [45] (as discussed in section 1.1.2.1). A program of shorter duration may not achieve levels of training required to detect changes in clinical outcomes of interest.

### 2.7 What is the proposed frequency and duration of follow up?

Study subjects will be followed for 6 months after enrollment. All subjects will attend study visits at Baseline, 3 months and 6 months after enrollment **(see Table 3: Study Visits pg. 12s).** We considered adding a visit at 12 months to assess long-term adherence to the exercise program and persistence of effect, however we felt that this would unduly lengthen the duration of our pilot study.

### 2.8 What are the proposed primary and secondary outcome measures?

As this is a pilot trial, rather than assigning primary and secondary outcomes, we have established feasibility indicators and clinical outcomes of interest.

**Feasibility indicators (measured throughout trial)**

1. Proportion of patients screened who are eligible to participate in the trial
2. Proportion of eligible patients who consent to participate in the trial
3. Proportion of subjects who are adherent with the intervention (see section 2.13. for measures of adherence)
4. Proportion of subjects who complete the trial

**Clinical outcomes (measured at Baseline, 3 months and 6 months)**

1. Venous disease-specific QOL
2. Generic QOL
3. Severity of PTS
4. Leg (triceps surae) strength
5. Leg flexibility
6. Time-on-treadmill (note: measured at pre-randomization and 6 months)

We decide against measuring the following outcomes: Hemodynamic measures of venous function e.g. venous filling time, venous pressures: Difficult to quantify reliably, machines not readily available, correlation between measures and patient symptoms is poor to moderate [62]. Full cardio-pulmonary exercise testing ($VO_2$ max): Expensive, and increasing maximal exercise capacity is not the goal of the proposed intervention and would be of uncertain clinical relevance in this population [63]. Further, as the ability to perform exercise is dependent on both changes in $VO_2$ max and individual anaerobic threshold [64], we feel that time-on-treadmill is a better and simpler measure of exercise capacity.

### 2.9 How will the outcome measures be measured at follow up?

**1. Venous Disease-Specific Quality of Life (Baseline, 3 mths, 6 mths)**: Venous disease-specific QOL will be assessed using the VEINES-QOL questionnaire, developed by our group, which is designed for self-completion and has been validated in English and French [65]. The questionnaire consists of 25 items (questions) that measure venous symptoms, limitations in daily activities due to venous disease, psychological impact of venous disease and change over the past year. VEINES-QOL has undergone comprehensive psychometric evaluation and has been shown to be acceptable, reliable, valid and responsive for use as a patient-reported measure of outcome in chronic venous disease (including PTS) [65] and acute DVT [66]. Our group has extensive experience using this measure in a number of completed [9-12] and ongoing multicenter studies.

**2. Generic Quality of Life (Baseline, 3 mths, 6 mths):** Generic quality of life will be measured using the Short-Form Health Survey-36 (SF-36) instrument [67,68]. The SF-36 is the current gold standard

measure of generic quality of life, has been used in numerous studies and has been validated in many languages. Two summary scores are produced: Physical (PCS) and Mental (MCS) Component Summary scores, which reflect physical and mental health status, respectively.

**3. Severity of PTS: (Baseline, 3 mths, 6 mths)**: Villalta's scale [59] has been used in a number of studies, including our own, to diagnose and grade severity of PTS [9,10,69,70] and is the only validated PTS scale available. This scale rates the severity, from 0 to 3, of five patient-reported symptoms and six clinician-observed signs. Points for symptoms and signs are summed into a total score. Patients will be categorised as having no PTS (score 0-4), mild PTS (score 5-9), moderate PTS (score 10-14) or severe PTS (score > 14 or presence of ulcer). In addition, the Villalta score will be analysed on a continuum (range 0-33).

***See Appendix for copies of above questionnaires, administration and scoring procedures.***

**4. Leg strength (Baseline, 3 mths, 6 mths):** Although in our training program we will strengthen the quadriceps, hamstring, gastrocnemius and soleus, there are no appropriate simple strength tests for these muscles. Proper strength testing of most muscle groups requires precise positioning and is expensive and time consuming [71-74]. We will therefore measure only the gastrocnemius/ soleus complex, the muscle that is most often affected by PTS. Its function is easily and reliably measured (ICC = 0.93 for test-retest reproducibility) using a simple test of muscle fatiguability/ endurance that our group developed [49]. In brief, the foot is positioned in a device and the heel is lifted to a height such that the navicular bone contacts a bar placed at a fixed height of 5 cm. The heel is then lowered. The movements are repeated 23 times/minute to the cadence of a metronome. The test is terminated when the subject can no longer achieve the required heel lift height or the required cadence. The total number of heel lifts performed is counted.

**5. Leg flexibility (Baseline, 3 mths, 6 mths):** Flexibility of quadriceps, hamstring, gastrocnemius and soleus muscles will be measured using standard positions and a gravity-based goniometer (inclinometer) with digital read-out [75]. For all maneuvers, a greater angle indicates greater flexibility. Detailed description of flexibility measurement procedures is provided in **Table 4, pg. 12t.**

**6. Time-on-treadmill (Pre-randomization, 6 mths)**: Exercise capacity at Pre-randomization and at 6 months post-intervention will be measured by using a standardized Bruce Ramp protocol [61]. The ramp treadmill protocol has identical workloads at equivalent time periods as the commonly-used Bruce protocol but allows for a more gradual increase in intensity. Maximal treadmill time with this protocol accounts for 86% of the variance in peak aerobic power. Time on test will be recorded.

### 2.10 Will health service research issues be addressed?

Quality of life is an important endpoint to evaluate when studying chronic symptomatic disorders such as PTS. Our clinical outcomes therefore include both disease-specific and generic QOL. We do not provide formal power calculations for the QOL outcomes as this is a pilot trial intended to measure effect size, among other aims. We will not perform a formal economic evaluation, however this could be considered for our future large multicenter trial.

### 2.11 What is the proposed sample size and what is the justification?

This pilot project is aimed at (1) determining the feasibility of our design and intervention in patients with PTS and (2) generating effect sizes for the clinical outcomes of interest to help calculate sample size for the larger, multicenter trial. For reasons of practicality and cost, we will limit the size of our study to 44 subjects (22 each group). We anticipate that the probable primary outcome for the larger trial will be change in venous-disease specific QOL, as measured by VEINES-QOL, however the other clinical outcomes we will measure in this pilot trial are of comparable interest. Our sample size of 44 subjects would provide a 95% confidence interval half-width of approximately +/– 2.4 assuming a standard deviation of 4 for VEINES-QOL scores [66].

### 2.12 What is the planned recruitment rate?

Potential subjects will be screened from among patients attending Thrombosis Clinics in Montreal (Jewish General Hospital, with additional referrals from Montreal General and St. Mary's Hospitals: **see letter of collaboration, Dr. S. Solymoss**) and Ottawa (Ottawa Civic Hospital). Study coordinators will use a Screening Log to record patient initials, age, sex, and reasons for exclusion (if applicable) for all patients approached. The Screening Log will be faxed to the Coordinating Site monthly to track rates of recruitment at each site. At present, there are 60 patients with PTS followed at the Jewish General Hospital clinic, 20 each at Montreal General and St. Mary's Hospitals and 60 patients at the Ottawa Civic Hospital. In addition, as all patients diagnosed with DVT are treated and followed at these clinics, newly incident cases of PTS arise weekly. Hence, we do not anticipate difficulty in recruiting the 44 subjects we require. In a recent trial of a motorized leg device to treat severe PTS (typically 10-15% of cases of PTS are severe), 12 such patients were recruited in 4 months at one Montreal site. There are no current or anticipated competing trials of PTS treatment.

The overall trial duration will be 2 years: 8 months (July 2006– Feb 2007) to create case report forms, develop the database and data entry interface, obtain Research Ethics Committee (REC) approval at both sites and begin to recruit patients with PTS; 10 months (March 2007–Dec 2007: aim to avoid cold winter months) to complete recruitment and carry out the interventions in all recruited patients; and 6 months (Jan 2008-June 2008) to clean and analyze data, report results and begin work on designing the larger multicenter trial.

**2.13 Are there likely to be any problems with compliance?**

We believe that patients with PTS will be very motivated to comply with the exercise intervention as treatments for this condition are severely limited. Frequent exercise supervision by exercise physiologists in the first few months will provide positive reinforcement. Providing each subject with their own heart rate monitor is expected to engage interest and participation and provides an element of control and reassurance. However, an important feasibility objective of this pilot trial is to evaluate the level of compliance with the Active Training intervention and reasons for poor adherence. Compliance with exercise will be assessed primarily via subject-completed exercise logs which will be completed following each exercise episode (whether supervised or performed independently) and will include information on type of exercise activity performed, frequency, duration and average intensity (heart rate achieved or Borg scale rating of perceived exertion [76]). Similar logs have been used successfully in previous trials of exercise training [45,53,54]. Compliance will also be evaluated by recording attendance at the supervised exercise sessions. In addition, as a means of evaluating compliance in the Active Training group and potential contamination in the Attention Control group, we will quantify habitual physical activity levels at Baseline, 3 and 6 months using the interviewer-administered version of the validated "short-form last 7 day recall" International Physical Activity Questionnaire (IPAQ) [56].

We decided against using pedometers or accelerometers to measure compliance, as these depend heavily on the subject wearing the device at all exercise sessions and add unnecessary complexity and expense.

**2.14 What is the likely rate of loss to follow up? On what evidence is this rate based?**

An important feasibility objective of this pilot trial is to evaluate rate of (and reasons for) loss to follow-up. In a recently completed cross-over trial (Kahn, Kearon co-investigators) that compared 2 fairly cumbersome battery-powered devices worn on the leg daily in patients with severe PTS, the drop-out rate (20 week follow-up) was 19%. In trials of exercise training programs of similar duration to our program, rate of loss to follow up was 7% in the Padberg study of older patients with chronic venous insufficiency [45] and ranged from 0-15% in trials of patients with arterial claudication [77-79].

**2.15 How many centres will be involved?**

This pilot trial will be conducted in 2 centres, in Montreal and in Ottawa. We considered performing a single-center pilot, but as we eventually intend to conduct a larger multicenter trial, we

believe it is important to demonstrate that our study is feasible in more than one centre.

### 2.16 What is the proposed type of analyses?

The objectives of this pilot trial are to assess the feasibility of the design and to measure the effect size of the intervention. Hence, the analyses will be primarily descriptive.

For feasibility indicators, we will describe rate of eligibility (proportion of patients screened who fully meet eligibility criteria to participate in the trial), rate of consent (proportion of eligible patients who consent to participate in the trial) and rate of loss-to-follow up (proportion of subjects who drop out of the trial, in total and by intervention group). We will also describe level of compliance in the Active Training group, calculated as the ratio of the number of exercise sessions reported or attended to the number of sessions prescribed, as has been used in other studies [45,53,79]. We will consider that our trial was feasible if the following criteria are met: rate of eligibility >30%, rate of consent >30%, rate of loss-to-follow up <20% and level of compliance > 60%. We will carefully review reasons for non-eligibility, lack of consent, drop-out and lack of compliance.

For clinical outcomes, we will describe change (means and standard deviations) in the Active Training and Attention Control groups, from Baseline to 6 months, in the following continuous measures: VEINES-QOL scores, SF-36 MCS and PCS scores (SF-36 scores are expected to improve with exercise "non-specifically" [50]), Villalta PTS severity score (will also be examined by category of severity), number of heel lifts performed (leg strength), stretch angles achieved for quadriceps, hamstring, gastrocnemius and soleus muscles (leg flexibility), and time-on-treadmill (exercise capacity). Each change score will be interpreted for clinical significance, based on published literature where available. In exploratory analyses, we will assess (1) whether there are associations between change in VEINES-QOL scores or in PTS severity and change in leg strength, leg flexibility or time-on-treadmill; (2) the impact of covariates such as age, sex, initial severity of PTS, baseline habitual activity, use of ECS or level of compliance on change scores; and (3) whether changes noted at 3 months are predictive of changes at 6 months. We acknowledge that the small size of this pilot study limits the validity of the findings of such exploratory analyses; we will guard against overinterpretation of such analyses.

Our analyses will provide important information on the expected feasibility and effect size of the interventions, which will be used to help design the full trial and determine its sample size.

### 2.17 What is the proposed frequency of analyses?

The analyses described above will be performed once, at the end of the trial.

### 2.18 Are there any planned subgroup analyses?

There will be no formal subgroup analyses. However, feasibility indicators and the magnitude of the effect size associated with the active intervention will be examined descriptively in various patient subgroups (according to level of compliance, study centre, initial PTS severity, baseline physical activity, use of ECS) to aid with the design of the larger multicenter trial.

### 2.19 Has any pilot study been carried out using this design?

Although we have not piloted the exact design proposed for the EXPO Pilot Trial, we have performed preliminary work that has contributed to the design and procedures of our proposed trial:

- We have completed and published previous pilot work on exercise in patients with DVT and PTS [40,42,48] as detailed in Section 1.1.2.2.
- Our group developed [65] and validated [65,66] the venous-disease specific QOL measure (VEINES-QOL) to be used in the trial, and we have used this measure in many previous studies.
- Our group designed a simple, inexpensive apparatus to standardize the heel rise test for calf muscle strength that will be used in the proposed trial. We showed that this device has high test–retest

reliability [49] and we successfully used the device in a study of 41 patients with DVT [40].

- Dr. Shrier (co-applicant), as PI of a CIHR-funded randomized trial of exercise training to improve functional status of patients awaiting total hip arthroplasty, has had direct experience designing and implementing an exercise program similar to the one we propose.

## 3. TRIAL MANAGEMENT

### 3.1 What are the arrangements for day to day management of the trial?

The trial will be coordinated from the Centre for Clinical Epidemiology at the Jewish General Hospital where Dr. Kahn (PI) is based. The Trial Coordinator (TC), supervised by the PI, will be responsible for the daily operations of the study, hence prior experience coordinating multicenter trials is essential. The TC's many responsibilities are detailed on pg. 1 of "Details of financial assistance requested" (Budget module). Study nurses at both sites will carry out patient screening, recruitment and will perform assessments at the Baseline, 3 & 6 month follow-up visits. They will receive training on questionnaire administration, assessment of PTS severity and use of the digital inclinometer and heel-lift device. Randomization of subjects, liaising with exercise physiologists to set up the first appointment for subjects randomized to Active Training and delivery of the Attention Control intervention will be performed by different research staff than those performing outcome assessments. Data management and on-line randomization will be overseen by Dacima Software Inc., a company that has developed a comprehensive electronic data management platform for healthcare research. Data will be entered on-line using a customized web-based data entry tool that will be adaptable at very low cost for the future larger, multicenter trial. Data quality will be maintained via validation checks at the time of data entry. Data will be reviewed and cleaned by the database coordinator on an on-going basis by initiating and following up on queries to the sites. The cleaned database will be provided to the biostatistician for analysis, which will be carried out under the supervision of Drs. Shapiro and Kahn.

### 3.2 What is the role of each principal applicant and co-applicant?

Our research team consists of experienced investigators in the domains of VTE, PTS, QOL, exercise physiology, exercise training, statistics and clinical trial methodology. Many of us hold career investigator salary awards for our research programs and have led or participated in multicenter thrombosis trials. We hold a number of CIHR and HSFC grants relating to venous thrombosis and have collaborated successfully on ongoing and past research projects, some relevant to this proposal. In addition to our evident strength in thrombosis research, Dr. Kahn is a recognized expert in PTS and QOL in venous disease, Dr. Shrier is a sports medicine physician with a PhD in exercise physiology who has previously led clinical trials of exercise training, Dr. Kearon is a thrombosis expert who also holds a PhD in exercise physiology, Dr. Reid is a scientist with the Prevention and Rehabilitation Centre of the University of Ottawa Heart Institute with experience in trials of exercise training for cardiac rehab and other medical conditions, Dr. Hirsch is a pulmonologist who has collaborated with Dr. Kahn on exercise studies in DVT patients and Dr. Shapiro is an experienced clinical trialist and biostatistician. The affiliations and specific roles of each applicant and collaborator are shown in Table 5 pg. 12u.

### 3.3 Describe the trial steering committee and the data safety and monitoring committee.

The trial Steering Committee (SC) will meet by phone regularly and on an as-needed basis to monitor trial progress, assess the need for changes in procedures and address issues that could affect the integrity or projected timeframe of the trial. The SC will be chaired by Dr. Kahn and will include all co-applicants. SC members will participate in the planning of the larger multicenter trial. A Data Safety Committee (DSC) will be established consisting of an experienced thrombosis physician and an exercise physiologist not involved with the trial. All serious adverse events and deaths will be notified to the Trial Coordinator within 48 hours of their occurrence. These will be forwarded to the DSC on an ongoing basis. The DSC will present any concerns regarding trial safety to the SC and the Research Ethics Boards.

**Figure 1. EXPO PILOT TRIAL: Study Schema**

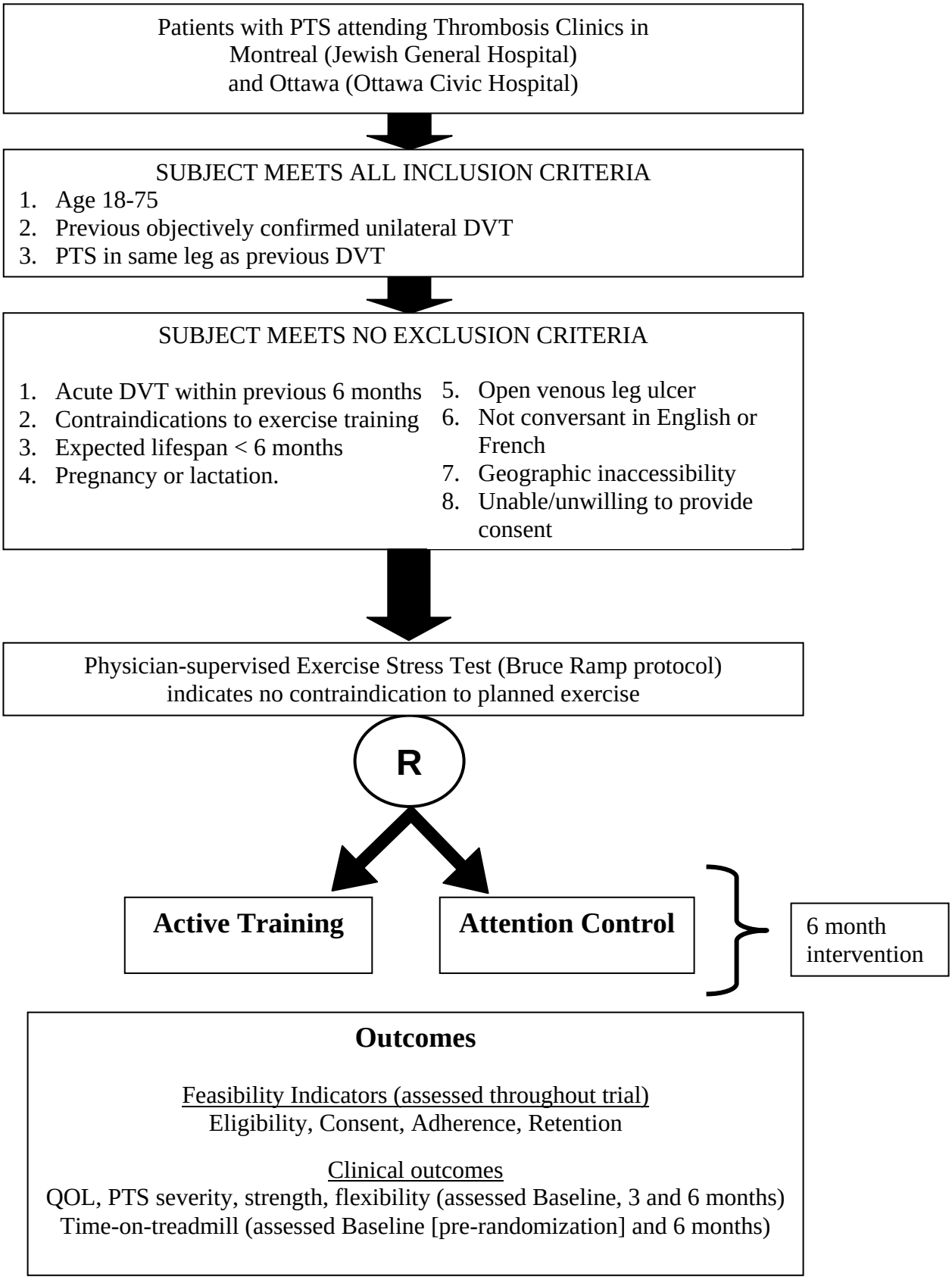


**Table 1. Detailed literature search strategy.**

All searches were performed week of March 1, 2006.

| Type of citation | Strategy | Result |
|---|---|---|
| **Systematic review** | Using the "Find Systematic Reviews" function of PubMed Clinical Queries, we conducted a computer database search for systematic reviews of the use of exercise to treat PTS. We combined the terms (postthrombotic syndrome OR postphlebitic syndrome OR venous insufficiency) AND (exercise OR exercise training) AND (systematic [sb]). | No citations were retrieved. |
| **Published clinical study** | To search for individual published studies (including trials) of exercise to treat PTS, we used the "Search for clinical studies of therapy" function of PubMed Clinical Queries, combining the terms (postthrombotic syndrome OR postphlebitic syndrome OR venous insufficiency) AND (exercise or exercise training) in a broad, sensitive search of English language clinical studies. | 13 articles were retrieved: 3 were our own clinical studies, described in section 1.1.2.2 [40,42,48], 1 was a cohort study of raised leg exercises for leg edema (of any cause) in the elderly, and 1 was the Padberg trial of exercise to treat chronic venous insufficiency [45], discussed in Section 1.1.2.2. The remaining 8 studies were not relevant as they did not pertain to PTS or to the use of exercise as a treatment intervention. Hence, no trials of exercise to treat PTS were retrieved. |
| **Registered clinical trial** | We searched clinical trial registries (www.clinicaltrials.gov; www.controlled-trials.com; http://isrctn.org) using the search terms postthrombotic syndrome OR postphlebitic syndrome OR venous insufficiency. | No trials of exercise to treat PTS (whether actively recruiting or closed to recruitment) were registered. |

**Table 2. Detailed description of Active Training intervention**

| **1. STRETCHES** | |
|---|---|
| ***General instructions:*** *To improve range of motion, we will use standard static stretching exercises. Each stretch is applied until the subject feels tension in the muscle and it is then held until the tension is no longer felt. This varies from 10s to 60s depending on the individual and muscle being stretched [80]. The subject then increases the stretch until they feel the same tension as initially, and the stretch is held for the same period of time. Stretches are performed at least once daily, but subjects are allowed to stretch more often if they wish to. The quadriceps muscle will be stretched in the side-lying position, the hamstring muscle will be stretched while the subject is sitting on a chair, the gastrocnemius muscle will be stretched in the standing position with the knee straight and the soleus muscle will be stretched in a crouched position with the knee bent. Different positions will be used if the preferred position causes discomfort.* | |
| **Quadriceps side-lying**: The subject bends the knee and holds the ankle. The lower limb is then pulled posteriorly to extend the hip and the stretch is felt in the anterior thigh (quadriceps muscle). It is important for the subject to maintain proper back posture and not arch the back. Although this stretch can be done standing, the side-lying position places less stress on balance capability. |  |
| **Hamstring**: The subject sits on a chair with the lower limb extended in front and the knee straight. The subject then bends forward at the hip and keeps the back straight. The stretch is felt in the posterior thigh (hamstring muscle). This stretch is normally shown with the subject sitting on the floor. However, inflexible subjects find this difficult because the floor position requires that the hip can be flexed to 90 degree and this is not possible for some subjects. |  |
| **Gastrocnemius**: The subject stands with the limb to be stretched posteriorly (right leg in photo). The knee is kept straight and the subject leans forward by dorsiflexing the ankle; the heel should be kept in contact with the floor and the stretch is felt in the posterior calf (gastrocnemius muscle). |  |
| **Soleus**: The soleus muscle has the same insertion as the gastrocnemius (Achilles tendon) but originates below the knee. Therefore, ankle dorsiflexion with the knee straight will tighten up the gastrocnemius muscle before placing any stress on the soleus; stretching the soleus muscle requires that the knee is bent. This stretch is often shown in the standing position. However, the alternative position, shown in the adjacent photo, allows the same stretch and prevents the need to support the entire body weight with the knee bent and thereby reduces knee stress. |  |

**Table 2, con'd. Detailed description of Active Training intervention**

## 2. STRENGTHENING

***General instructions**: We will use the approach of traditional fitness programs and prescribe 3 sets of 10 repetitions with a 1-min rest between sets. Strengthening exercises will be performed every other day. If all three sets of 10 are completed easily, the intensity of the exercise will be increased. If the person cannot complete the first set of 10, or achieves 5 or fewer repetitions on the third set, the intensity will be decreased or we will reduce the number of repetitions per set. Further, there should be no more than minimal pain or discomfort during the exercise, which should subside within 5 minutes of completing the exercise session. If pain occurs outside of these boundaries, the intensity, duration, or number of repetitions will be decreased depending on the particular stage of the program.*

*The method of increasing intensity when a training effect is observed depends on the particular exercise. We will strengthen the quadriceps and hamstring muscles using the wall squat; this movement requires both knee extension (quadriceps) and hip extension (hamstring). Lowering the body further along the wall, switching to a single-leg wall squat or adding dumbbell weights to the hands increases intensity. We will strengthen gastrocnemius/soleus muscles using the standing heel-raise exercise; the subject is standing and lifts their heels off the ground by plantarflexing the ankle as much as possible. The body weight is then lowered slowly back to the standing position. Switching to one leg or performing the exercise with the heel over the edge of a stair (so that the ankle achieves greater than 90 degrees of dorsiflexion) increases the intensity.*

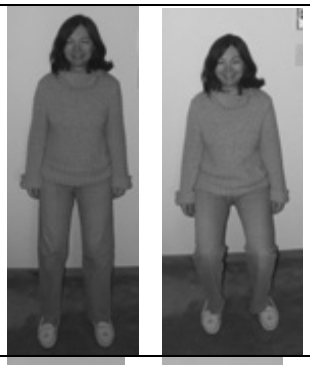
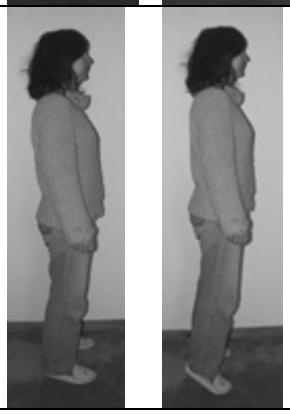
| | |
|---|---|
| Knee Extensors (quadriceps) and Hip Extensor (hamstring). The patient begins with the back against the wall and slowly lets the back slide down keeping the knees aligned with the first toe (i.e. avoid knee valgus). The depth of the squat depends on the conditioning of the patient. When strong enough, exercise intensity will be increased by doing wall squats on one leg only and then by adding dumbbell weights to the hands. |  |
| Gastrocnemius/Soleus. The deconditioned subject begins with standing on two legs and raises the heels off the ground. The body is then slowly lowered while standing only on the affected leg. When strong enough, the body is raised and lowered only on the affected leg. Further progression is achieved by standing with the heel over the edge of a stair. The body is now lowered so that the ankle achieves greater than 90 degrees of dorsiflexion. |  |

**Table 2, con'd. Detailed description of Active Training intervention**

## 3. AEROBIC PROGRAM

- Because swimming does not use the calf muscles, and cycling only uses the calf and hamstring muscles when appropriate technique is used, we have opted to use a walking-jogging program so that we can target all potentially affected muscles. Some subjects may prefer to jog and others may prefer to only walk. If deemed appropriate by the exercise physiologist and preferred by the subject, other weight bearing exercises could replace the walk/jog, for example an aerobic dance tape, step class or team sports such as basketball, volleyball.
- We will personalize the program so that it is enjoyable for each subject but still achieves a training effect. For example, we can increase the intensity of the aerobic walking program by including hills rather than progressing to jogging.
- Exercise will be prescribed by the exercise physiologist at each site. The intensity level (velocity of walking-jogging, inclusion of hills), duration (exercise time for each session) and frequency (number of exercise sessions per week) will vary depending on the initial conditioning of the subject and on the weekly improvement in fitness. Similar guidelines for increasing exercise intensity, duration and frequency will be followed by the exercise physiologists at each site.
- The exercise prescription will be individualized and will follow guidelines from the American College of Sports Medicine (ACSM) for developing and maintaining cardiorespiratory fitness [51]. These guidelines suggest that individuals perform 60-120 minutes/week of aerobic exercise within their target heart rate zone (60-85% of maximal heart rate). Duration is dependent on the intensity of the activity. Frequency of sessions and the mode of aerobic exercise will also be individualized.
- For deconditioned subjects, we will begin with 15 min of aerobic exercise daily and increase this to 30 min over the course of the exercise program.
- Programs will be tailored to the individual depending on severity of PTS, accessibility to equipment, time constraints, and enjoyment of various activities.
- The intensity of the exercise will begin at 60-70% of maximal heart rate for all individuals and will gradually be increased to as high as 75-85%, depending on the subject's adaptation to the exercise. For example, some subjects will have no difficulty walking quickly (75% of maximal heart rate) 4 times a week for 30 minutes/session, whereas others will need to walk slowly (60%) for 10 minute sessions twice daily.
- The progression will depend on the baseline fitness and the response to the exercise program. To prevent any injury, we will only increase total exercise by 10-20% per week. Therefore, if hills are introduced into the aerobic program (representing an increase in intensity), then either the velocity or duration or frequency will be reduced so that the entire program over the week is not increased beyond 10-20%.

**Table 3. Study visits and procedures**

The planned visits and procedures are shown in the chart below.

| | Baseline Visit | 3 month Visit | 6 month Visit |
|---|---|---|---|
| **ALL SUBJECTS** | | | |
| Baseline Case Report Form (CRF) | X | | |
| Follow-up CRF | | X | X |
| PTS severity | X | X | X |
| Generic QOL | X | X | X |
| Venous disease-specific QOL | X | X | X |
| Calf muscle strength | X | X | X |
| Leg muscle flexibility | X | X | X |
| Time-on-treadmill | X (pre-randomization EST) | | X |
| IPAQ activity questionnaire | X | X | X |
| Serious adverse event form | Completed for all serious adverse events | | |
| Withdrawal form | Completed for patients who withdraw from the study | | |
| Death form | Completed for patients who die during follow-up | | |
| **SUBJECTS IN ACTIVE TRAINING GROUP** | | | |
| Sessions with exercise physiologist | Duration & frequency as described in Research Proposal (section 2.2.1.) | | |
| Exercise logs | Completed by subject after each session of exercise | | |
| **SUBJECTS IN ATTENTION CONTROL GROUP** | | | |
| 1-hour education session on PTS | Within 2 weeks of randomization | | |
| Phone calls to subject by Research Coordinator | Monthly | | |

**Table 4. Description of muscle flexibility measurement procedures.**

All measurements will be performed using an inclinometer with digital read-out. For all maneuvers, a greater angle indicates greater flexibility.

| Muscle group | Measurement technique |
|---|---|
| **Quadriceps** | Subject is placed in the prone position so that the hip is extended; the knee is gradually flexed until the pelvis rotates anteriorly due to the pull of the rectus femoris component of the quadriceps muscle (attaches to the anterior inferior iliac spine of the pelvis). In this position, 0º represents a tibia that is parallel to the table (inability to bend the knee) and 90º represents a tibia that is perpendicular to the table (increased quadriceps flexibility). |
| **Hamstring** | Subject is placed in the supine position, the hip is bent to 90º and the knee is bent to 90º. The knee is then gradually extended until resistance is felt. To remain consistent with greater angles representing greater flexibility, we will record the angle in relation to the femur; 90º is when the tibia is perpendicular to the femur and 180º is when the knee is straight and the tibia is in line with the femur. |
| **Gastrocnemius and soleus** | The same position as that used to stretch the muscle will be used. We will record 0º as the position where the tibia is perpendicular to the floor and measure the flexibility as the angular displacement of the tibia when the ankle is dorsiflexed (a larger angle reflects increased flexibility). Range of motion when the knee is straight represents the gastrocnemius flexibility and when the knee is bent represents the soleus flexibility. |

## Table 5. Affiliations and specific roles of applicants and collaborators

***Principal Investigator***

**Susan Kahn MD MSc,** Departments of Medicine and Epidemiology & Biostatistics, McGill University, Montreal. Role: Study design (expertise in thrombosis, PTS, QOL, epidemiology), overall study coordination and decision-making, coordination and patient recruitment at Jewish General Hospital site, Chair of Steering Committee.

***Co-Investigators (alphabetical order)***

**David Anderson MD,** Department of Medicine, Dalhousie University, Halifax. Role: Study design (expertise in thrombosis, trial design), Steering Committee member.

**Andrew Hirsch MD**, Division of Pulmonary Medicine, Department of Medicine, McGill University, Montreal. Role: Study design (expertise in thrombosis, exercise testing), patient recruitment at Jewish General Hospital site, Steering Committee member.

**Clive Kearon MD PhD**, Department of Medicine, McMaster University, Hamilton, Ontario. Role: Study design (expertise in thrombosis, muscle and cardiovascular physiology, exercise testing, trial design), Steering Committee member.

**Mike Kovacs MD,** Department of Medicine, University of Western Ontario, London, Ont. Role: Study design (expertise in thrombosis, trial design), Steering Committee member.

**Robert Reid, PhD MBA,** Department of Medicine, University of Ottawa Scientist, Prevention and Rehabilitation Centre, University of Ottawa Heart Institute. Role: Input into design of exercise program, overseeing implementation of exercise training program, Ottawa subjects.

**Marc Rodger MD MSc,** Departments of Medicine and Epidemiology, University of Ottawa. Role: Study design (expertise in thrombosis, trial design), coordination and patient recruitment at Ottawa Hospital site, Steering Committee member.

**Stan Shapiro PhD**, Biostatistician and Clinical Trialist. Department of Epidemiology and Biostatistics, McGill University, Montreal. Role: Study design, statistical, methodological expertise and clinical trial expertise, Steering Committee member.

**Ian Shrier MD PhD**, Departments of Family Medicine and Epidemiology & Biostatistics, McGill University, Montreal. Role: Study design (expertise in exercise and muscle physiology, exercise training and evaluation), design, oversight and supervision of exercise training program and measurement of physiological outcomes, Steering Committee member.

**Phil Wells MD MSc**, Departments of Medicine and Epidemiology, University of Ottawa. Role: Study design (expertise in thrombosis, trial design), coordination and patient recruitment at Ottawa Hospital site, Steering Committee member.

***Collaborators***

**Susan Solymoss MD** Hematologist, McGill University Health Centre, Montreal. Role: Recruitment of trial participants from Thrombosis Clinics at McGill University Health Centre hospitals.

**Ilka Lowensteyn PhD.** Exercise Physiologist and Medical Scientist, Department of Medicine, McGill University. Role: Input into design of exercise program, coordination of exercise stress testing and overseeing implementation of exercise training program, Montreal subjects.

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