OFFICIAL TITLE: PHYSICAL ACTIVITY IN CHILDREN AT RISK OF POST- THROMBOTIC SYNDROME: A PILOT RANDOMIZED CONTROLLED TRIAL

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Abbreviations Table:

ACCP	American College of Chest Physicians
BMI	Body mass index
CBC	Complete blood count
CHST	Children's Health System of Texas
CT	Computed topography
CTEPH	Chronic thromboembolic pulmonary HTN
DVT	deep vein thrombosis
eCRF	Electronic Case Report Form
ECS	Elastic Compression Stocking
ED	Emergency Department
FMH	Family medical history
HEENT	Head, eyes, ear, nose, throat
HTC	Hemostasis Thrombosis Center
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society of Thrombosis and Haemostasis
MRI/MRA	Magnetic resonance imaging/magnetic resonance angiography
PE	Pulmonary embolism
PHI	Protected Health Information
PTS	Post thrombotic syndrome
QOL/Peds QL	Quality of Life/Pediatric Quality of Life
ROC	Receiver Operator Curve
SOC	Standard of Care
TEG	Thromboelastography
TG	Thrombin generation
TGP	thrombin generation potential
VTE	Venous thromboembolism

BACKGROUND AND RATIONALE

Venous thromboembolism (VTE) is a major and growing problem in children. A 70% increase in the annual rate of VTE in hospitalized children has been documented in the past decade[1]**.** VTE often collectively referred to as deep venous thrombosis (DVT) and pulmonary embolism (PE), is now considered an important endemic complication of tertiary care settings. Although often perceived as an acute disorder, VTE entails a long-term risk of persistent or progressive thrombosis, post-thrombotic syndrome (PTS), recurrence and post-PE syndrome, also called chronic thromboembolic pulmonary hypertension (CTEPH)[2]. Of all the VTE outcomes, PTS is the most frequent, chronic and debilitating complication[3]. As such, current therapy is merely focused on treating the acute VTE, not attempting to prevent late sequelae like PTS. Despite appropriate anticoagulation, up to one half patients will develop these poor complications within 2 years of the acute event[4].

VTE is not merely a 'nuisance' medical problem. *Rather, VTE is costly and burdensome to patients and society*, both in terms of dollars spent and effect on quality of life and productivity[5]. The estimated health care costs directly attributable to pediatric VTE for care of secondary VTE are five times higher than costs with an idiopathic VTE ($95,120 vs. $20,238)[5]. These costs are expected to be much higher in the presence of adverse outcomes of thrombosis[6].

Although **PTS is a direct and most frequent DVT complication in children, effective treatments are lacking and new innovative approaches to manage PTS are sorely needed**. The 9th edition of the American College of Chest Physicians (ACCP) guidelines on antithrombotic Therapy in Neonates and Children, widely considered to represent the standard of care for pediatric thrombosis do not currently have any recommendations for management of pediatric PTS[7]. Recently, the American Heart Association issued a scientific statement to provide an up-to-date overview of PTS and concluded, *"as a result of the paucity of studies in this area, it is not possible to make specific recommendations on the prevention or treatment of pediatric PTS*", highlighting this as an area in pressing need of scientific investigation[8]. Despite receiving early detection and appropriate anticoagulation, up to a quarter to one half of DVT patients develop PTS[3]. Lack of effective and evidence-based treatment for PTS is a

source of difficulty and frustration for patients with PTS and clinicians alike. I propose that using technology to alter behavior and implement life style interventions may help curb the epidemic of DVT and its outcomes.

Background

PTS is the most frequent and debilitating complication after extremity DVT

The annual rate of VTE- encompassing DVT and PE- has increased by 70% in hospitalized children in the past decade, to approximately 1 in 200[1, 6]. Accompanying this increase is the attendant increase in chronic sequelae of VTE, the most frequent of which is the PTS. PTS is the most burdensome complication of DVT. The lasting signs and symptoms of PTS include chronic pain, cramping, swelling, varicose collateral veins and in extreme cases, painful venous ulcers[9]. Children with PTS have an impaired QoL[10].

Children at risk of or with PTS do not have any effective, evidence-based treatments available

In contrast to the gains achieved in treating acute DVT, there are very few treatment options for PTS in children. Clinicians often prescribe physical compression methods to counteract increased venous pressure. However, the SOX trial, the largest randomized trial so far of elastic compression stockings in adults did not prevent PTS with two years of use after a first proximal DVT[11]. Venoactive medications and surgical treatments for PTS such as venous valve repair or venous bypass have primarily been evaluated in small adult series only[12, 13]. Novel approaches to the treatment are sorely needed.

Enhancing activity post DVT represents a new paradigm for pediatric PTS

The pathophysiology of PTS involves: 1) damage to venous valves by thrombus or by associated inflammatory mediators[14], which causes valvular reflux; and 2) residual venous obstruction due to thrombus persistence leading to impaired venous return[15, 16]. Both processes result in venous hypertension. When DVT is diagnosed, standard anticoagulation treatment prevents clot extension and embolization, but does not lyse the acute clot. Follow-up studies of patients with DVT treated with anticoagulants have shown only partial clearance of thrombus and even in patients who do achieve clot lysis, permanent

damage to the valve occurs. This is thought to be via thrombus induced activation of inflammation or scarring associated with acute and resolving thrombosis, leading to valve incompetence as shown in studies of adults[14]. Aerobic activity increases oxygen delivery to muscle fibers, improves muscle metabolism and oxidative capacity[17]. It is plausible that this may counteract the hypoxic damage to muscle contractile fibers and decreased muscle perfusion caused by venous hypertension[18]. It may aid faster venous recanalization by improving blood flow. Indeed, adult data show a tendency for higher levels of self-reported physical activity in 300 patients one month after DVT to be associated with less severe PTS three months later, suggesting that increasing physical activity may reduce symptoms of PTS[19]. Similarly, in another 2-center Canadian pilot study, 42 adults with PTS were randomized to 6 months of exercise training or control. Supervised exercise training was associated with improvement in PTS severity, QoL, leg strength and leg flexibility[20]. The potential benefits of enhanced physical activity have not been previously studied in the pediatric setting.

Activity trackers show promise in incentive based activity trials in children
While previous efforts have relied on self-report measures to increase activity, more recently direct and objective fitness trackers have been used to track population levels of physical activity in children and adolescents[21, 22]. One such tracker, the Fitbit has shown high correlation with steps recorded by an accelerometer, accuracy when compared to a gold standard pedometer and has been validated[23]. Recent studies show that tailored intervention, such as responses and messaging created to address the needs of individuals on baseline steps/day maybe efficient and effective[24, 25]. Indeed, daily step target to measure physical activity in children has been shown to increase as a result of participating in activity tracker-based interventions in conjunction with daily step goals and incentives[26].

Conceptual model of endothelial dysfunction and impaired fibrinolysis supports biomarker assessment in PTS
The overall progression of the initial thrombotic event towards propagation or resolution depends on the balance between: 1) endothelial dysfunction and inflammation, and 2) residual venous obstruction from impaired fibrinolysis. Standard anticoagulation relies upon endogenous fibrinolytic

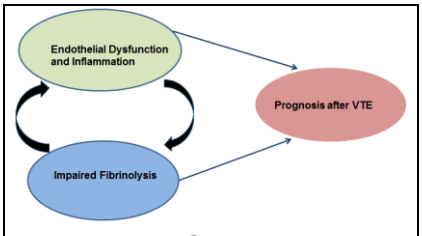


Figure 1: Conceptual pathophysiological model underlying PTS.

mechanisms to remove thrombus, which are often impaired in children with DVT[27]. Even in those who achieve clot lysis, permanent damage to venous valves occurs frequently, likely via thrombus-induced activation of inflammation[14]. *I propose that a bidirectional relationship between inflammation and abnormal fibrinolysis drives a feedback loop resulting in increased complications after DVT over time, including PTS* **(Figure 1).** Bringing together this insight and our current knowledge of coagulation assessment by global assays -focusing on PTS- may uncover new and better approaches to identify and treat at-risk individuals. Exercise has shown to decrease thrombin generation and fibrinolytic markers in children as well as adults. Alterations in the level of related biomarkers, reflecting coagulation activation, inflammation and markers of fibrinolysis, may be of interest when assessing a patient's risk of developing PTS.

Extrapolating from the above, I propose that an activity regimen for children after lower extremity DVT is unlikely to be harmful, maybe of benefit and needs further study. In the past, investigator initiated trials involving prevention or treatment of pediatric VTE have been terminated because of feasibility concerns[28]. Accordingly, a pilot study to establish feasibility of this approach is required before proceeding to a fully powered, definitive trial.

INNOVATION

This proposal is innovative because: (1) it will be the *first* trial to integrate modern technological tools, such as activity trackers to improve adherence to life style interventions aimed at preventing PTS. Although there are many ways to increase physical activity in children, my goal is to use a simple, user-friendly tool that will appeal to children across a broad age range; (2) activity/exercise as a therapeutic modality in children with DVT has not been previously studied; (3) there have been no previous randomized trials of PTS prevention or treatment in children; and (4) trial outcomes include patient reported outcomes (i.e. QoL) and laboratory based biomarkers.

PRIMARY AIM:

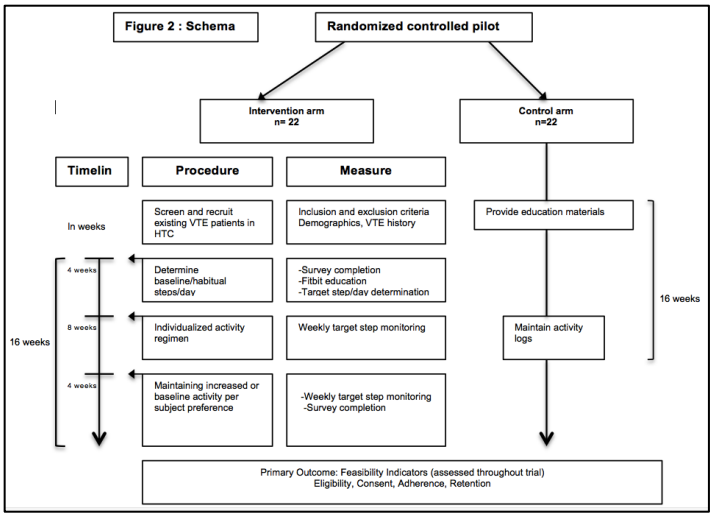
To demonstrate the feasibility and potential effectiveness of a personal "fitness tracker" to improve adherence to an activity regimen following an initial DVT in children.

Hypothesis: The intervention of using a fitness tracker to adhere to an activity regimen will be acceptable, and effective in improving adherence

to a post-DVT activity regimen in children. I propose a validated, fitness tracker, the Fitbit, to improve adherence to a 16-week activity regimen in a pilot randomized controlled trial (RCT), in which 44 subjects with DVT will be assigned to the intervention group or to a comparison group. The primary outcomes will consist of a) feasibility indicators determined *a priori* (eligibility, consent, adherence, retention) and b) estimates of effect size associated with the prescribed activity regimen, by describing within-subject change in QoL and 'potential' biomarkers of PTS pre and post intervention in each group.

STUDY DESIGN (Figure 2)

The study design is that of a pilot RCT to test the feasibility of the proposed activity tracker to increase activity in children post DVT, against standard practice, which currently consists of providing education about PTS and instructions to 'be active'. I will use a validated activity tracker, the Fitbit and its data platform- the Fitabase.



METHODS

I. STUDY SETTING

All newly diagnosed patients with first, lower extremity DVT diagnosed at Children's Health System of Texas (CHST) or referred to the Hemostasis Thrombosis Center (HTC) at CHST who have completed 12 weeks (±2 weeks) of anticoagulation therapy, will be approached for recruitment.

II. ELIGIBILITY CRITERIA

Parents must provide written, informed consent before any study procedures occur.

INCLUSION CRITERIA	RATIONALE
1. Age 7-21 years	VTE is seen across all age groups
2. A radiologically confirmed, acute, proximal (iliofemoral and femoropopliteal) first lower extremity DVT and/or confirmed,	Population with proximal DVT and/or PE deemed to be at highest risk of PTS

acute pulmonary embolism (unilateral or bilateral)	
3. 12 weeks (±2 weeks) after starting anticoagulation	To mitigate the small theoretical risk of clot dislodgement with activity soon after DVT diagnosis
4. Out-patient ambulatory status	Protocol involves increasing activity

EXCLUSION CRITERIA	
1. Contraindication to increasing activity such as patients with juvenile arthritis, poor balance, congestive heart failure etc.	Protocol involves increasing activity

III. STUDY PROTOCOL

The study has 3-4 planned visits, which will coincide with the standard of care visits.

Screening

The parents/legal guardians will be given an explanation about the study and informed consent and/or assent will be obtained. This may occur in the inpatient or the outpatient setting. Demographic information and relevant medical history, including results of scans and thrombophilia testing will be collected. All medications, including anticoagulant medication received for the thrombotic event will be recorded.

a. Baseline Assessments (collected as SOC (standard of care)):

i. History and Physical Examination:

1. Detailed history regarding medical disorders predisposing to thrombosis and potential triggers (birth control pills, recent travel or surgery or immobility) and predispositions (thrombophilia, obesity etc.) will be collected.
2. Review of existing medical records recorded on Children's Medical Center electronic medical record to review past medical, family and social history will be performed.
3. Comprehensive physical exam (PE) consisting of vital signs, general appearance, head, eyes,

ears, nose, throat (HEENT), cardio-respiratory, abdominal, extremities and skin will be performed at each visit as per standard of care.

ii. Laboratory:
    1. Complete blood count (CBC), reticulocyte count, baseline coagulation studies, and a comprehensive thrombophilia panel performed as SOC will be recorded.

iii. Treatment:
    1. Information on anticoagulant therapy (medication of choice, intensity of anticoagulation, planned duration of therapy) prescribed as per the treating physician will be collected for subjects who meet eligibility criteria and whose parents provide written informed consent

iv. Radiological:
    1. All information related to site, extent and venous segments involved of the thrombotic venous segment at the time of diagnosis, and at completion of therapy will be collected. Information on reflux assessment at the time of end of therapy ultrasound will also be collected.

v. Assessment of **Post-thrombotic syndrome (PTS):** All subjects with will be assessed with standardized, validated outcome assessment tools: the Manco-Johnson Instrument and the modified Villalta scale starting at 6 months post diagnosis of DVT as per standard of care. See appendix 1 for these scales.

b. Study Interventions:

i. Study procedures/Randomization:

Eligible, consenting subjects will be individually randomized via a web-based program to the Fitbit arm or the control arm (1:1 allocation ratio).

1. **Intervention (Fitbit) arm.** The intervention arm will wear a Fitbit for a 16-week period (**Figure 2)**. General Principles of an aerobic activity regimen:

As the principal muscles affected by PTS are the lower limb muscles, we have opted to use a walking-jogging program to capture steps/day by the Fitbit. This will target all potentially affected muscles (quadriceps, hamstrings ad gastrocnemius/soleus). If preferred by the subject, other weight bearing exercises could replace the walk/jog, for example, dancing or team sports such as basketball or volleyball. Because of the unfamiliarity with activity trackers, subjects will be provided with hands-on training to promote successful use of the Fitbit and Fitabase.

a. Schedule and procedures **(Table 1)***:* After consent (baseline visit), subjects in this arm will receive a standardized 15-20 minute education session on PTS (what constitutes PTS, why patients get it, how to manage it) and enhanced activity after DVT. Subjects will be asked to wear the Fitbit for a period of four weeks to establish baseline or 'habitual' activity. Using steps/day data received at the end of four weeks, we will determine an individualized activity prescription of 'target
steps/day', corresponding to a 25% increase above the baseline.

Table 1	**Visit 1**	**Visit 2**	**Visit 3**
	12 wks post DVT Dx (±2 weeks)	16 wks after Visit 1 (±4 weeks)	8 wks after Visit 2 (±4 weeks)
	SOC Visit	SOC Visit	SOC Visit (Exit Visit)
ALL SUBJECTS			
Informed Consent	X*		
Full Medical History and Exam	X	X	
Biomarker Testing^	X$	X	X
FVIII, D-dimer, CRP	X	X	X^^
QOL forms	X	X	X
PTS Assessment		X	X
ECS and Log	X	X~	X~
Activity Logs/ Questionnaire	X	X	X
Medication Log***	X	X	X

Phone Calls (monthly)	X	X	
Formal Education Session	X		
Honoraria**	X	X	X
SUBJECTS IN FITBIT ARM			
Hands on Fitbit Training	X		
Steps/Day Data (weekly)	X	X	X
Phone Calls (weekly)	X	X	
Return Fitbit			X

*Informed consent can occur any time after DVT diagnosis until Visit 1; ^Biomarker testing includes: D-Dimer, FVIII, Thrombin generation, markers of fibrinolysis; $Biomarker testing at Visit 1 may be combined with other SOC labs for those still on anticoagulation at this time; ~ only ECS logs; ** $25 at Visit 1 and 2, and $50 at Visit 3; ***Medication logs only for participants on Rivaroxaban or Xarelto; ^^Factor VIII, D-dimer, and CRP can be completed as research procedures at Visit 3 for participant's whose values were within normal range at Visit 2.

Subjects will be asked to maintain the target steps/day for a period of 8 weeks. At the end of this period, subjects will either maintain the increased activity or resume habitual activity for another 4 weeks, per patient preference. A phone call will be made periodically for encouragement and to ensure adherence to the activity regimen throughout the initial 16-week period. Subjects will have another visit 8 weeks (±4 weeks) after the end of the 16-week period corresponding to the ~ 9 month post-diagnosis SOC visit. For subjects having difficulty with the activity prescription or use of the Fitbit, a phone call or face-to-face session will be arranged with the study research coordinator and physical therapist. Such changes will be carefully documented.

2. **Control arm.** The control intervention will consist of: 1) a standardized 15-20 minute education session on PTS (what constitutes PTS, why patients get it, how to manage it) and benefits of enhanced activity

(activity will not be specifically addressed and will be up to the choice of the subject) after DVT; 2) monthly phone contacts will be made to check in with patients/families and remind them about completion of activity logs and follow-up visits.

Study assessments for both arms

1. *Biomarker testing:* Blood for biomarker of coagulation activation (D-dimer, FVIII, thrombin generation), markers of inflammation (CRP), and markers of fibrinolysis {modified thromboelastogram (TEG) with fibrinolysis, PAI-1, will be obtained at each visit One and a half extra teaspoons will be collected at each visit for a total of 4.5 teaspoons collected during the subject's time in the study.
2. Elastic compression stockings (ECS)
    i. Subjects in both arms will be provided with custom fitted compression stockings and their use will be tracked using ECS logs throughout study period. In general, SOC recommendations are to wear ECS starting after the diagnosis of DVT and to continue as long as they provide benefit in regards to pain and swelling, up to a period of two years post DVT diagnosis. For the sake of the study, their use will be documented strictly during the study period.
3. Activity log completion during the intervention period will be used to record physical activities. These logs will capture information on the type of activity, and the frequency and duration of activity
4. *Quality of life (all visits):* QoL will be measured using the PedsQL ™ which is a modular approach to measure generic health related quality of life in both healthy children and adolescents, as well as those with acute and chronic health conditions. It consists of structured interview with the parents and the child with 23 items divided among 4 sub-scales to assess function in 4 domains: Physical; Emotional; social; and School. The instrument is brief, takes 15

minutes to administer, and is developmentally adjusted for a broad age range.

5. PTS : Modified Villalta's scale and Marilyn-Manco Johnson Instruments, the two validated PTS scales, will be used to diagnose and grade severity of PTS at the 6 month mark corresponding to Visit 2 and the 9 month mark (corresponding to Visit 3). The principal and co-investigators will complete PTS evaluations as is standard of care at Visit 2 and Visit 3. In addition, a blinded PTS assessment will also be completed by the physical therapist (currently routinely assigned to the Thrombosis and Bleeding Disorders Program) at both visits.
6. Medication adherence: Anti-Xa and INR will be collected for participants on lovenox and warfarin, respectively. Families with participants on Rivaroxaban will be asked to complete a medication log because no assay will be used to measure adherence for Rivaroxaban. The medication log will measure compliance with anticoagulation during active treatment period and will include the subject's specific anticoagulant, dose, and date and time medication was taken.

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

IV. PARTICIPANT TIMELINE

All study visits will coincide with standard-of-care visits for patients with VTE at our center. All visits will be allowed a time window to accommodate preferences of subjects and families ± 2 weeks for visit 1 and ±4 weeks for visit 2 and 3.

Study assessments: **(Table 1 for schedule of events).**

V. MODIFICATIONS

a. RISKS

i. Blood Draws: Risks associated with drawing blood include minimal discomfort and/or bruising, infection,

excess bleeding, clotting, and/or fainting are possible.

ii. Doppler Ultrasound: There are no risks from the sound waves used for ultrasound. The test is not painful and does not have any radiation. This will be done as per standard of care.

iii. Skin irritation or allergies with wearing the activity tracker

iv. Injuries or falls related to increased physical activity

v. As we plan to use an online data format to gather subject information, security of information may be a concern. Fitabase code and databases reside on the Microsoft Windows Azure Platform and rely on the robust security, both physical on-premise guarding, and over network, provided as part of that platform. Windows Azure runs in data centers that comply with key industry standards for security and reliability.

vi. Loss of confidentiality related to use of protected health information (PHI).

b. BENEFITS

Study subjects may discontinue their participation at any time. However, information regarding the potential benefits to continue on the study will be made explicitly clear prior to their discontinuation.

i. Whether or not the subject or their family consents, the schedule of the clinic visits will remain the same as proposed in the study. All patients with thrombosis are followed until they become adults with more frequent visits in the first 24 months after the acute event and then yearly afterwards.

ii. Subjects will also derive benefit from the careful monitoring of activity after thrombosis as well as interval telephone calls to promote compliance and answer questions.

iii. Successful monitoring after the acute thrombotic event is expected to improve their overall well-being and possibly prevent any physical, cardiac, cognitive and behavioral abnormalities resulting from thrombosis.

iv. Subjects will be provided with custom fitted compression stockings as part of the study. Compression stockings help to relieve swelling and pain and reduce the risk of developing post-thrombotic syndrome after a DVT. Although prescribed for all post DVT patients, many do not use them due to the expense of the stockings and lack of availability.

c. Every effort will be made to retain study subjects in the trial for the entire ~9 months to enable complete follow-up and data collection.

V. WITHDRAWAL/TERMINATION

a. Subjects that 'No Show' for Visit 2, are unable to provide >80% of the 'steps/day' data and are unable to be contacted/rescheduled. Data already collected will be used in the analysis.

b. Subjects for whom an alternative diagnosis discovered.

c. In the investigator's medical opinion, it is best to withdraw the subject from the protocol

VI. CONCOMITANT CARE

a. Patients who initially receive thrombosis care elsewhere prior to enrollment may participate in the study if all eligibility criteria are met.

b. Subjects who need to continue long term prophylactic anticoagulation will still be eligible and will be included at discretion of their attending hematologist.

c. The activity tracker, the Fitbit, is made up of a flexible durable material used in many sports watches (and one that does not contain latex) with a surgical grade stainless steel clasp and contains traces of nickel. It is meant to be worn day and night on the wrist. Because there's a possibility of skin irritation and allergies with any type of jewelry, all participants in this study will be warned and care and wearing tips will be provided. They will be monitored for any skin problems during the clinic visits and a treatment plan will be made in collaboration with their primary pediatrician should any skin irritation develop. I will ask to be notified immediately of any such occurrence at home and will then contact the participant or the family to assess

their clinical condition and make a treatment plan based on the severity of the skin condition.

VII. OUTCOMES AND POWER CALCULATIONS

Primary Outcomes will be 1) **feasibility indicators (Table 2)** measured throughout trial. The level of adherence in the intervention group will be calculated as the proportion meeting the weekly steps/day goal during the 'active' 8-week period of the total 16 weeks of intervention as determined by the Fitabase data platform output, and 2) change in **clinical outcomes** such as PTS biomarkers at baseline and Visit 2, and QoL (at all visits). Secondary outcome: I will assess for PTS with validated scales at the 6 and 9 month follow-up visit as is standard of care.

Table 2: Feasibility Indicators

Proportion of screened subjects who meet eligibility criteria: ≥ 30%
Proportion of screened subjects who provide consent: ≥ 30%
Level of adherence in the intervention arm: ≥ 60%
Proportion of subjects who complete the trial: ≥ 80%

Analyses: The objectives of this trial are to assess the feasibility of the design and to measure the effect size of the intervention. All analyses will therefore be descriptive and will be performed once, at the end of the trial. Means and standard deviations, or when appropriate, medians and semi-inter-quartile ranges will be used to describe demographic and clinical characteristics. Reasons for non-eligibility, lack of consent, dropout and lack of compliance will be documented. For feasibility indicators, we (study investigators and Song Zhang-biostatistician) will describe rate of eligibility (proportion of subjects screened who fully meet trial eligibility criteria to participate in the trial), rate of consent (the proportion of eligible subjects who consent to participate) and rate of loss to follow-up (proportion of randomized subjects who drop out of the trial, in total, and by allocated intervention). We will also describe the level of compliance in the intervention group, calculated as the ratio of who complied with the activity prescription to the number given the prescription. We will consider the trial *successful* if the following criteria are met: rate of eligibility ≥ 30%, rate of consent ≥ 30%, rate of loss of follow-up <20%, level of compliance ≥ 60% and proportion of subjects who complete the trial ≥ 80%. For the clinical outcomes (including the secondary outcomes), we will describe change (means and standard deviations) in the intervention and control groups, from baseline to 6 month, in the QoL scores and PTS biomarkers. Each change score will be interpreted for clinical significance and common responses counted for frequency of occurrence. The impact of the activity

tracker to promote continued physical activity in the last 2 weeks of the 12-week period would be explored. We will also assess the impact of covariates such as age, sex, BMI, baseline activity, intensity of activity over and above the activity prescription, on change scores.

Sample size calculation*:* For reasons of practicality and cost, we have decided to limit the size of this pilot RCT to 44 subjects (20 in each arm; 22 after considering a 20% drop out rate). We anticipate that the probable primary outcome for the larger trial will be change in rate of PTS development and/or progression. This trial may also provide compelling preliminary data for future studies. For example, if this intervention reduces the risk of PTS from 26% (known probability of PTS) to 10%, this pilot study has 71% chance of showing a promising trend (p-value<0.2) that the intervention reduces the risk of PTS. We acknowledge that the small size of this pilot study limits the validity of the findings; therefore, we will be cautious with such analyses.

I. RECRUITMENT

a. Information about the clinical study will be provided via direct communication by study investigators and physicians at Children's Medical Center including ED physicians, hospitalists, and general pediatricians attending on the inpatient medicine services and outpatient continuity clinic as well as house officers.
b. Information regarding the study will be available on the University of Texas Southwestern clinical trials website and at clinicaltrials.gov.
c. Potential subjects will be identified through review of new patient referrals to Children's Medical Center, inpatient admissions and/or consultations for thrombosis.
d. Each subject will receive financial compensation for participation. Payment will be made at completion of the study visits at Visits 1 and 2 ($25 each) and at the end of Visit 3 ($50) based on attendance and return of the tracking logs.
e. Expected recruitment rate will be 2-3 participants per month.
f. Duration of recruitment period is expected to be approximately 24 months.

g. Assessment of study recruitment and retention will be performed when 20 participants have been enrolled on the study, or at approximately 9 -12 months.

II. DATA COLLECTION, MANAGEMENT AND ANALYSIS

a. DATA COLLECTION METHODS

Clinical information will be collected from each patient's electronic medical record at all visits while on study. This information will include the following: name, gender, race, ethnicity, date of birth, current medications, social history, patient medical and hospitalization history; family history, physical exam and laboratory results. Additional information to be collected from self reported diaries include adherence data and adverse reaction data. Returned diaries will be maintained in a research binder, while medical history, lab results, and medications will be recorded in the electronic medical record and then on electronic Case Report Forms (eCRF). Contact phone numbers for parents and relatives will be collected for the interim visit phone calls.

b. DATA MANAGEMENT

The eCRF will be housed in UT Southwestern REDCap. REDCap is a self-managed, secure, web-based data support system. The data is backed up offsite nightly and hosted in a secure environment maintained by Information Resources. This password protected study database will include a subject's personal identifiers and all Protected Health Information (PHI) such as medical history. All personnel who will be accessing the data will be trained in REDCap and have individual user ID and passwords. Subjects will have a study ID number that will be utilized in lieu of personally identifiable information for all research data provided to statisticians.

c. STATISTICAL ANALYSES

The following will be calculated: the proportion of screened patients who fully met trial eligibility criteria, the proportion of eligible patients who consented to participate, the proportion in the physical activity/ Fitbit group who adhered to prescribed activity, and the proportion of randomized patients who completed the trial (in total, and by allocated intervention). The feasibility outcomes will be reported descriptively

using mean (standard deviations [SD]) for continuous outcomes, and raw counts (%) for categorical outcomes are reported. For the clinical end points, using an intent-to-treat analysis that includes all participants with data at baseline and 6 months (end of the intervention period), within-patient change from baseline (diagnosis or pre-VTE levels) to 6 months (mean, SD) in the physical activity will be compared to standard care in the following measures: D-dimer, FVIII, CRP, thrombin generation assay parameters of endogenous thrombin potential and peak thrombin, fibrinolysis on thromboelastography, QoL (total and physical), selfreported physical activity levels, and PTS (change from 6 to 9 months). This will be averaged for each group, and within-group differences will be compared between the standard care and physical activity groups using a t test. ECS use will be descriptively described but not included in a formal analysis.

ETHICS AND DISSEMINATION

I. RESEARCH ETHICS APPROVAL

This protocol and template informed consent forms will be reviewed and approved UT Southwestern IRB with respect to scientific content and compliance with applicable research and human subjects regulations. Subsequent to initial review and approval, the investigators will submit progress reports to the IRB at least annually and at study closure.

II. PROTOCOL AMMENDMENTS

Any modifications to the protocol, which impact the conduct of the study, or potential risk/benefit of the participants, will require a formal amendment to the protocol with IRB approval.

III. CONSENT OR ASSENT

Informed consent will be obtained after information has been provided to patients' families along with a discussion of the risks and benefits along with opportunity for questions. Consent forms will be provided for all parents involved in the trial.

IV. CONFIDENTIALITY

Records of each patient's participation in this study, including the original informed consent document, will be kept in a locked file cabinet in the Center for Cancer and Blood Disorders at Children's Medical Center. Access to local

research files is limited to treating physicians and nurses, data management personnel and the Institutional Review Board. These entities may need to view data for quality assurance and data management purposes. Confidentiality of all medical records would be maintained by correct identification of the appropriate person before viewing the medical record and ascertaining the reason for the viewing of the medical records.

V. DECLARATION OF INTERESTS

Ayesha Zia, MD, No financial or other competing interests.

VI. ACCESS TO DATA

All trial investigators will be given direct access to the data sets.

VII. ANCILLARY AND POST TRIAL CARE

Participants who develop adverse outcomes of thrombosis upon study completion will receive treatment at discretion of their provider.

VIII. DISSEMINATION POLICY

Every attempt will be made to reduce the interval between completion of data collection and the release of the study results. We expect to take about 3 to 4 months to compile the final results and submit them for presentation at a prominent society meeting and publication in a high profile peer reviewed journal. The study results will also be released to the participating physicians, referring physicians, subjects and the general medical community.

APPENDICES

Appendix 1 - Components of the standardized outcome measures for post thrombotic syndrome (PTS) employed in pediatric studies, including the Manco-Johnson Instrument (A) and the modified Villalta scoring system (B).

Appendix 2 - Health-Related Quality of Life (QoL) Instruments

Appendix 3 – Medication Administration Log (For participants on Rivaroxaban)

Appendix 4 – Electronic Compression Stocking Log

Appendix 5 – Activity Log/questionnaire *(Initial and Follow Up), Godin questionnaire*

Appendix 1

A- Manco-Johnson Instrument (MJI)

PHYSICAL FINDINGS

Please measure to nearest tenth of one centimeter

Limb Circumference Measurements	Right	Left
Mid-proximal limb	_____.____ **cm**	_____.____ **cm**
Mid-distal limb	_____.____ **cm**	_____.____ **cm**

Basic CEAP Mark an "X" where applicable/present.

Physical Findings	Right	Left
0. No visible or palpable signs of venous disease		
1. Swelling, with or without pitting edema		
2. Dilated collateral circulation of extremity only		
3. Skin changes ascribed to venous disease (i.e., pigmentation, venous eczema)		
4. Skin changes as in 3 with ulceration or superior vena cava syndrome		

FUNCTIONAL FINDINGS (Pain Symptoms)

Wong-Baker Faces Pain Rating (Oucher Scale: Score 0-5 for each)

Pain Outcome: Wong-Baker (Oucher) Scale	Right	Left
With aerobic exercise only		
With activities of daily living		
At rest		

If pain is present (i.e., score 1-5): Does the pain interfere with activities?
YES NO

Comments:

_____

_____

Aerobic exercise only: Implies that symptoms are present only when child engages in vigorous age-appropriate sport such as running, lap swimming, soccer, basketball or volleyball.

Activities of daily living: Implies that a child is symptomatic when engaging in ordinary age-appropriate activities in the home, school and community short of organized sports and vigorous aerobic activities. These symptoms limit and alter a child's ordinary day-to-day activities such as walking at school, shopping with the family or participation in a birthday party.

At rest: Implies a constant presence of symptoms that is independent of activity. The child's daily life is severely limited by symptoms.

Signs	
Edema	1
Dilated superficial collateral veins	1
Venous stasis dermatitis	1
Venous stasis ulcers	1

Symptoms Chronic lower-extremity pain • Limiting aerobic activities • Limiting activities of daily living • At rest	 0-5 0-5 0-5
Post Thrombotic Syndrome absent	0
Any Post-Thrombotic Syndrome present	≥ 1
Physically and functionally significant PTS	Signs ≥ 1 and Symptoms ≥ 1

B- Modified Villalta Score

Symptoms *Pain or abnormal use* *Swelling*	 1 1
Signs Increased limb circumference Change in skin color Pitting edema Venous Collaterals on skin Pigmentation of skin Tenderness on palpations of deep veins Varicosities Head Swelling Ulceration	 1 1 1 1 1 1 1 moderate; 2 severe 1 moderate; 2 severe 9
Mild Post-Thrombotic Syndrome	1-3
Moderate Post-Thrombotic Syndrome	4-8
Severe	≥ 9

Components of the standardized outcome measures for post thrombotic syndrome (PTS) employed in pediatric studies, including the Manco-Johnson Instrument (A) and the modified Villalta scoring system (B).

Appendix 2

Health-Related Quality of Life (QoL) Instruments

General QoL:
The PedsQL ™ is a modular approach to measure generic health related quality of life in both healthy children and adolescents, as well as those with acute and chronic health conditions. It consists of structured interview with the parents and the child with 23 items divided among 4 sub-scales to assess function in 4 domains: Physical; Emotional; social; and School. Each item is a statement of a problem, which the subject rates in severity from 0-4, indicating a problem never occurs (score of 0) to almost always occurs (score of 4). The instrument is brief, takes 15 minutes to administer, and is developmentally adjusted for a broad age range.

Venous Disease-Specific QoL
The VEINS-QoL is a venous disease specific QoL tool that has been validated in adults with DVT and PTS. This is a 26-item questionnaire that measures the impact of DVT and PTS on symptoms and quality of life from the patient's perspective. The item covers symptoms (10 items), limitations on daily activities (9 items), time of day of greatest intensity (1 item), change over the past year (1 item), and psychological impact (5 items).

Scoring of QoL Instruments
Scoring of PedsQL ™

Description of the questionnaire

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores indicate better health related QoL
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	5	1-5	1-5	

Scoring of Dimensions

Item Scaling	**5-point Likert scale from 0 (Never) to 4(Almost always)**
Weighting of items	**No**
Extension of the scoring scale	**Scores are transformed on a scale from 0-100**
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50,3=25,4=0 **Step 2: Calculate Scores** Score by Dimensions • If more than 50% of the items in the scale are missing, the scale scores should not be computed • Mean Score= Sum of the items over the number of items answered <u>Psychological Health Summary Score</u>= sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. <u>Physical Health Summary Score</u>= Physical Functioning Scale Score Total Score: Sum of all the items over the number of items answered on all the scales.
Interpretation and Analysis of missing Data	If more than 50% of the items in the sacle are missing, the Scale Scores should not be computed If 50% or more items are completed: impute the mean of the completed items in a scale

Appendix 3

DAILY MEDICATION ADMINISTRATION LOG

Name: Medication:

.

Date Given	Dose	Times per day	Reactions and Side effects*	Reason For not taking med	Other Notes

*nose bleeds, mouth bleeding, GI bleeding, heavy periods, bruising, burning and pain with shots, hair loss

Appendix 4

COMPRESSION STOCKINGS LOG

Name:

Compression Stocking type: ☐ Knee-high ☐ Thigh-high ☐ Arm sleeve

Compression level: ☐ 15-20 mm Hg ☐ 20-30 mm Hg ☐ 30-40 mm Hg

Date Worn	Times per day worn	No of hours worn	Reactions and Side effects*	Other Notes

*Discomfort, worsening of pain, color changes, ulcers, difficulty wearing

Appendix 5

Physical Activity Questionnaire (Initial)

Start time: End time:

This is short survey to find out about your level of physical activity before and after you developed a blood clot. These includes sports or dance that make you sweat or make your legs feel tired, or games that make you breathe hard, like tag, skipping, running, climbing, and others.

Your answers will help us understand how a blood clot affects your ability to be active. We believe your answers will help us treat you and other children with blood clots better.

Remember:

1. There are no right or wrong answers- this is not a test.
2. Please answer all questions as honestly and accurately as you can- this is very important.

ID :_____
Age:_____

Sex: M_____ F_____
Grade:_____

BEFORE the diagnosis of a blood clot:
Answer the following questions for the time before you had a blood clot.

1. Were you involved in any physical activity?
   Yes ☐ No ☐

2. If yes, was this physical activity part of:

☐ Recreation/leisure (sports/game/exercise)
☐ Work/School
☐ Transportation

3. Were these activities organized competitive activities or sports? (Check one only.)
   No (or gym class only)……...☐

   Yes, but WITHOUT an official or judge (such as a club or pickup games)...☐

   Yes, with an official or judge…….....☐

   Yes, at a national or professional level…… ☐

   Not sure…… ☐

AFTER the diagnosis of blood clot:

1. Describe your current activity level.

   ☐ Unchanged

   ☐ Decreased

   ☐ Increased

2. If your overall activity is **increased** after the blood clot, what is the reason? If it is not increased, move to the next question.

Reason:

3. If your overall activity is **decreased** after the blood clot, what is the reason? Check all that apply. If it is not decreased, move to the next question.

   ☐ Leg pain

   ☐ Leg discomfort or heaviness

   ☐ Leg swelling

   ☐ Chest pain

   ☐ Trouble breathing

   ☐ No desire to be active

   ☐ Fear that the clot may move in my body

☐Other

4. If your overall activity is **decreased** after the blood clot, check one of the boxes below. If it is not decreased, move to the next question.

☐ Wholly inactive, dependent on others, and cannot leave residence

☐ Mostly inactive or restricted to minimum activities of daily living

☐Sometimes participates in mild activities, such as walking, limited housework and limited shopping

☐Regularly participates in mild activities

☐Sometimes participates in moderate activities such as swimming, or could do unlimited housework or shopping

☐Regularly participates in moderate activity as before

☐Regularly participates in active events, such as bicycling, bowling of golf

☐ Sometimes participates in impact sports such as jogging, tennis, football or heavy labor

☐ Regularly participates in impact sports

5. Were you sick in the past week (s), or did anything prevent you from doing your normal physical activities? (Check one.)

Yes ☐ No ☐

If yes, what prevented you? _____

Thank you for your time and participation. Please contact Dr. Zia or Dr. Journeycake at 214-648-3896 for any questions and concerns that you may have related to this questionnaire.

References:
Godin,G,. Shephard,R.J..(1997) Godin Leisure-Time Exercise Questionnaire. *Medicine and Science in Sports and Exercise. 29 June Supplement: S36-S38*
Kowalski, K.C., Validation of the physical activity questionnaire for older children. *Pediatric Exercise Science, 9, 342-352*

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

Times Per Week

a) STRENUOUS EXERCISE
(HEART BEATS RAPIDLY)
(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE
(NOT EXHAUSTING)
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE
(MINIMAL EFFORT)
(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1.	2.	3.

Thank you for your patience. You are almost done.

----------For Research Use:

1. Time taken to complete survey (minutes): _____
2. Subject's <u>Habitual</u> Physical Activity (i.e before the diagnosis of DVT):

   ☐ Mild (gardening, yoga, archery, fishing, bowling, golf, walking, swimming, snow mobiling)

   ☐ Moderate (dancing, baseball, bicycling, volleyball, badminton, cross-country skiing, skating)

   ☐ Strenuous (tennis, running, jogging, hockey, football, soccer, squash, basketball, alpine skiing, judo)

   ☐ Mostly Inactive

*If a subject has participated in activities qualifying for more than 1 intensity category, classify in the highest category

3. Godin Score before the diagnosis of VTE:

4. PAQ-C/ PAQ-A Score before the diagnosis of VTE:

5. Subject's Physical Activity as assessed at the current visit:
   ☐ None

☐ Mild (gardening, yoga, archery, fishing, bowling, golf, walking, swimming, snow mobiling)

☐ Moderate (dancing, baseball, bicycling, volleyball, badminton, cross-country skiing, skating)

☐ Strenuous (tennis, running, jogging, hockey, football, soccer, squash, basketball, alpine skiing, judo)

☐ Mostly Inactive

6. Godin Score after the diagnosis of VTE:

7. PAQ-C/ PAQ-A Score before the diagnosis of VTE:

8. Other comments:

Godin Leisure-Time Exercise Questionnaire

3. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

Times Per Week

d) STRENUOUS EXERCISE
(HEART BEATS RAPIDLY)
(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling) _____

e) MODERATE EXERCISE
(NOT EXHAUSTING)
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing) _____

f) MILD EXERCISE
(MINIMAL EFFORT)
(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking) _____

4. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. 👎	2. 👎	3. 👎

Thank you for your patience. You are almost done.

1. Describe your current activity level.

   ☐ Unchanged

   ☐ Decreased

   ☐ Increased

2. If you overall activity is **increased** since the last visit, what is the reason? If it is not increased, move to the next question.

   Reason:

3. If you overall activity is **decreased** since the last visit, what is the reason? Check all that apply. If it is not decreased, move to the next question.

   ☐ Leg pain

   ☐ Leg discomfort or heaviness

   ☐ Leg swelling

   ☐ Chest pain

   ☐ Trouble breathing

   ☐ No desire to be active

   ☐ Fear that the clot may move in my body

   ☐ Other

4. If your overall activity is **decreased** since the last visit, check one of the boxes below. If it is not decreased, move to the next question.

   ☐ Wholly inactive, dependent on others, and cannot leave residence

   ☐ Mostly inactive or restricted to minimum activities of daily living

   ☐ Sometimes participates in mild activities, such as walking, limited housework and limited shopping

   ☐ Regularly participates in mild activities

   ☐ Sometimes participates in moderate activities such as swimming, or could do unlimited housework or shopping

   ☐ Regularly participates in moderate activity as before

   ☐ Regularly participates in active events, such as bicycling, bowling of golf

   ☐ Sometimes participates in impact sports such as jogging, tennis, football or heavy labor

   ☐ Regularly participates in impact sports

5. Were you sick in the past week (s), or did anything prevent you from doing your normal physical activities? (Check one.)

   Yes ☐ No ☐

   If yes, what prevented you? _____

Thank you for your time and participation. Please contact Dr. Zia or Dr. Journeycake at 214-648-3896 for any questions and concerns that you may have related to this questionnaire.

For Research Use:

1. Time taken to complete survey (minutes)

2. Subject's Physical Activity as assessed at the current visit:
   ☐ None

   ☐ Mild (gardening, yoga, archery, fishing, bowling, golf, walking, swimming, snow mobiling)

   ☐ Moderate (dancing, baseball, bicycling, volleyball, badminton, cross-country skiing, skating)

   ☐ Strenuous (tennis, running, jogging, hockey, football, soccer, squash, basketball, alpine skiing, judo)

☐ Mostly Inactive

3. Godin Score:

4. PAQ-C/ PAQ-A Score:

5. Other comments:

For Research Use:

6. Time taken to complete survey (minutes):

7. Subject's Habitual Physical Activity (i.e before the diagnosis of DVT):

☐ Mild (gardening, yoga, archery, fishing, bowling, golf, walking, swimming, snow mobiling)

☐ Moderate (dancing, baseball, bicycling, volleyball, badminton, cross-country skiing, skating)

☐ Strenuous (tennis, running, jogging, hockey, football, soccer, squash, basketball, alpine skiing, judo)

*If a subject has participated in activities qualifying for more than 1 intensity category, classify in the highest category

8. Godin Score before the diagnosis of VTE:

9. PAQ-C/ PAQ-A Score before the diagnosis of VTE:

10. Subject's Physical Activity after the diagnosis of DVT:

☐ Mild (gardening, yoga, archery, fishing, bowling, golf, walking, swimming, snow mobiling)

☐ Moderate (dancing, baseball, bicycling, volleyball, badminton, cross-country skiing, skating)

☐ Strenuous (tennis, running, jogging, hockey, football, soccer, squash, basketball, alpine skiing, judo)

11. Godin Score after the diagnosis of VTE:

12. PAQ-C/ PAQ-A Score before the diagnosis of VTE:

13. Other comments:

References:

1. Raffini L, Huang YS, Witmer C, et al. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics 2009;124:1001-1008.
2. Goldenberg NA. Long-term outcomes of venous thrombosis in children. Current opinion in hematology 2005;12:370-376.
3. Goldenberg NA, Donadini MP, Kahn SR, et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. Haematologica 2010;95:1952-1959.
4. Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. Pediatric research 2000;47:763-766.
5. Kerlin BA. Current and future management of pediatric venous thromboembolism. American journal of hematology 2012;87 Suppl 1:S68-74.
6. Setty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. Pediatric blood & cancer 2012;59:258-264.
7. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e737S-801S.
8. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation 2014;130:1636-1661.
9. Hopkins NF, Wolfe JH. ABC of vascular diseases. Deep venous insufficiency and occlusion. Bmj 1992;304:107-110.
10. Kumar R, Rodriguez V, Matsumoto JM, et al. Health-related quality of life in children and young adults with post-thrombotic syndrome: results from a cross-sectional study. Pediatric blood & cancer 2014;61:546-551.
11. Kahn SR, Shapiro S, Ginsberg JS. Compression stockings to prevent post-thrombotic syndrome - Authors' reply. Lancet 2014;384:130-131.
12. Diehm C, Trampisch HJ, Lange S, et al. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet 1996;347:292-294.
13. Ackroyd JS, Browse NL. The investigation and surgery of the post-thrombotic syndrome. The Journal of cardiovascular surgery 1986;27:5-16.
14. Roumen-Klappe EM, den Heijer M, van Uum SH, et al. Inflammatory response in the acute phase of deep vein thrombosis. Journal of vascular surgery 2002;35:701-706.
15. Franzeck UK, Schalch I, Jager KA, et al. Prospective 12-year follow-up study of clinical and hemodynamic sequelae after deep vein thrombosis in low-risk patients (Zurich study). Circulation 1996;93:74-79.
16. Prandoni P, Frulla M, Sartor D, et al. Vein abnormalities and the post-thrombotic syndrome. Journal of thrombosis and haemostasis : JTH 2005;3:401-402.

17. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. The New England journal of medicine 2002;347:1941-1951.
18. Makitie J. Muscle changes in patients with varicose veins. Acta pathologica et microbiologica Scandinavica Section A, Pathology 1977;85:864-868.
19. Shrier I, Kahn SR. Effect of physical activity after recent deep venous thrombosis: a cohort study. Medicine and science in sports and exercise 2005;37:630-634.
20. Kahn SR, Shrier I, Shapiro S, et al. Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2011;183:37-44.
21. Lee JM, Kim Y, Welk GJ. Validity of consumer-based physical activity monitors. Medicine and science in sports and exercise 2014;46:1840-1848.
22. Tudor-Locke C, Lutes L. Why do pedometers work?: a reflection upon the factors related to successfully increasing physical activity. Sports medicine (Auckland, NZ) 2009;39:981-993.
23. Sasaki JE, Hickey A, Mavilia M, et al. Validation of the Fitbit wireless activity tracker for prediction of energy expenditure. Journal of physical activity & health 2015;12:149-154.
24. Carr LJ, Bartee RT, Dorozynski C, et al. Internet-delivered behavior change program increases physical activity and improves cardiometabolic disease risk factors in sedentary adults: results of a randomized controlled trial. Preventive medicine 2008;46:431-438.
25. Richardson CR, Brown BB, Foley S, et al. Feasibility of adding enhanced pedometer feedback to nutritional counseling for weight loss. Journal of medical Internet research 2005;7:e56.
26. Finkelstein EA, Tan YT, Malhotra R, et al. A cluster randomized controlled trial of an incentive-based outdoor physical activity program. The Journal of pediatrics 2013;163:167-172.e161.
27. Sharathkumar AA, Pipe SW. Post-thrombotic syndrome in children: a single center experience. Journal of pediatric hematology/oncology 2008;30:261-266.
28. Massicotte MP, Sofronas M, deVeber G. Difficulties in performing clinical trials of antithrombotic therapy in neonates and children. Thrombosis research 2006;118:153-163.