CONFIDENTIAL PROTOCOL

ACUTE VENOUS THROMBOSIS: THROMBUS REMOVAL WITH ADJUNCTIVE CATHETER-DIRECTED THROMBOLYSIS

THE ATTRACT TRIAL

Study Drug	Recombinant Tissue Plasminogen Activator (Activase)
IND Number	103462
Principal Investigator	Suresh Vedantham, M.D. Professor of Radiology & Surgery Mallinckrodt Institute of Radiology Washington University School of Medicine
Sponsor	Washington University School of Medicine St. Louis, Missouri
Protocol Version Number	Version 4.0
Protocol Version Date	February 14, 2013

Table of Contents

ABBREVIATIONS

ACCP	American College of Chest Physicians
AE	Adverse event
AVP	Ambulatory venous pressure
CAIRR	Cooperative Alliance for Interventional Radiology Research
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
cDNA	Complementary DNA
CDT	Catheter-directed intrathrombus thrombolysis
CEAP	Clinical-Etiologic-Anatomic-Pathophysiologic Classification
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment
CME	Continuing medical education
CPR	Cardiopulmonary resuscitation
CRF	Case report form
CT	Computed tomography
CV	Curriculum vita
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
eCRF	Electronic case report form
ECS	Elastic compression stockings
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GI	Gastrointestinal
HcG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-induced thrombocytopenia
ICH	International Conference on Harmonization
ICU	Intensive care unit

IND	Investigational drug exemption
INR	International normalized ratio
IRB	Institutional Review Board
IU	International units
IVC	Inferior vena cava
LMWH	Low molecular weight heparin
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
NS	Not statistically significant
PCDT	Pharmacomechanical catheter-directed intrathrombus thrombolysis
PCS	Physical Component Summary
PE	Pulmonary embolism
PHI	Protected health information
PMT	Percutaneous mechanical thrombectomy
PT	Prothrombin time
PTS	Post-Thrombotic Syndrome
PTT	Partial thromboplastin time
QALY	Quality-adjusted life-year QOL Quality of life
rt-PA	Recombinant tissue plasminogen activator
SAE	Serious adverse event
SF-36v2	Short-Form Health Survey-36, Version 2
SIR	Society of Interventional Radiology
UFH	Unfractionated heparin
UP	Unanticipated Problem
VCSS	Venous Clinical Severity Score
VETO	Venous Epidemiological and Thrombosis Outcomes Study
VEINES	Venous Insufficiency Epidemiological and Economic Study
VSDS	Venous Segmental Disease Score
VTE	Venous thromboembolism

PROTOCOL SYNOPSIS

Product Name: Activase (Recombinant Tissue Plasminogen Activator, rt-PA)		**Protocol Date**: February 14, 2013	
Title: Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (the ATTRACT Trial)			
Investigator/Sponsor: Suresh Vedantham, M.D.		**Institution:** Washington University in St. Louis	
Primary Objective: Determine if the initial adjunctive use of Pharmacomechanical Catheter-Directed Thrombolysis (PCDT) in symptomatic patients with acute proximal deep vein thrombosis (DVT) reduces the occurrence of the Post-Thrombotic Syndrome (PTS) over 24 months follow-up. **Secondary Objectives**: 1) Compare resolution of acute DVT symptoms; venous disease-specific and general quality of life (QOL); safety; and cost-effectiveness between the two treatment arms; 2) Identify pre-treatment predictors of heightened therapeutic response to PCDT via correlation of PTS scores and QOL change scores with demographical variables, DVT risk factors, symptom duration, and anatomic thrombus extent; and 3) Determine if PTS scores and QOL change scores are correlated with post-treatment thrombus burden, recurrent DVT, and valvular reflux.			
Number of Patients: 692		**Number of Centers:** 30-60	
Experimental Arm Treatment: PCDT with intrathrombus delivery of rt-PA (maximum allowable total dose 35 mg) into the DVT over a period of up to 30 hours. Three methods of initial rt-PA delivery will be used: 1) Trellis-8 Peripheral Infusion System – maximum first-session rt-PA dose 25 mg; 2) AngioJet Rheolytic Thrombectomy System – maximum first-session rt-PA dose 25 mg; or 3) Catheter-directed rt-PA infusion for up to 30 hours at 0.01 mg/kg/hr (maximum 1.0 mg/hr) via a multisidehole infusion catheter. Before and after PCDT, patients will receive standard DVT therapy as in the Control Arm. **Control Arm Treatment:** Initial anticoagulant therapy with unfractionated heparin, enoxaparin, dalteparin, or tinzaparin, for at least 5 days, overlapped with long-term oral warfarin (target INR 2.0 – 3.0). Elastic compression stockings will be prescribed.			
Inclusion Criterion: Symptomatic proximal DVT involving the iliac, common femoral, and/or femoral vein. **Exclusion Criteria:** Active bleeding; bleeding diathesis including INR > 1.6 or platelets < 100,000/ml; severe liver dysfunction; recent (< 3 months) internal eye surgery, GI bleeding, or hemorrhagic retinopathy; history of stroke or intracranial lesion; recent (< 10 days) surgery, CPR, trauma, obstetrical delivery, cataract surgery, or other major invasive procedure; pregnancy; active cancer except for non-melanoma primary skin cancers; massive pulmonary embolism; acute limb threat from DVT; hemoglobin < 9.0 g/dl; age < 16 years or > 75 years; severe hypertension; allergy to heparin, rt-PA, or iodinated contrast; life-expectancy < 2 years; chronic non-ambulatory status; moderate (diabetics) or severe (non-diabetics) renal impairment; index DVT symptom duration > 14 days; established PTS or previous symptomatic DVT within the last 2 years in the index leg; contralateral symptomatic acute DVT involving the iliac and/or common femoral vein or for which thrombolysis is planned for initial DVT therapy; recent (<5 days) use of thienopyridine antiplatelet drugs (except clopidogrel); inability to tolerate PCDT, provide informed consent, or comply with study assessments (e.g. due to cognitive impairment).			
Design: NIH-funded, Phase III, multicenter, randomized, open-label, assessor-blind, parallel two-arm, controlled clinical trial.			
Primary Efficacy Outcome: Cumulative incidence of PTS within 24 months after randomization (Villalta PTS Scale). **Secondary Efficacy Outcomes:** Severity of PTS (Villalta PTS Scale, CEAP Clinical Class, Venous Clinical Severity Score); disease-specific (VEINES-QOL/Sym measure) and general (SF-36, Version 2) QOL; resolution of presenting DVT symptoms (Likert Scale, calf circumference measurements, Villalta PTS Scale); prevalence of valvular reflux and residual thrombus at 1 year (Duplex ultrasound); degree of clot lysis with PCDT (venography, Experimental Arm only); and cost-effectiveness.			
Safety Endpoints: Major bleeding, symptomatic pulmonary embolism, recurrent venous thromboembolism, and death.			
Data Analysis: The Ontario Clinical Oncology Group's Clinical Trials Methodology Group at McMaster University in Hamilton, Ontario (Canada) will be the Data Coordinating Center for the study. The primary data analysis will be an intent-to-treat comparison of the cumulative incidence of PTS within the 24 months after randomization. A stratum-adjusted Cochran-Mantel-Haenszel test will be used, testing will be two-sided, and a p value of 0.05 will be considered significant.			
Trial Duration: 6.5 years	**Start Date:** November 2009	**Stop Date:** May 2016	**Publication:** Expected 2016

1 INTRODUCTION AND BACKGROUND

1.1 Disease Background: Impact of the Post-Thrombotic Syndrome (PTS)

The Post-Thrombotic Syndrome (PTS) is a frequent (25-50%) complication of proximal lower extremity deep vein thrombosis (DVT) (1-5). The clinical manifestations of PTS, which include chronic limb swelling, pain, heaviness/fatigue, pruritus, paresthesias, venous claudication, stasis dermatitis, and/or skin ulceration, cause major hardship to affected patients (6). The physical limitations of patients with PTS are comparable to those of patients with other severe chronic medical conditions – many patients are disabled, unable to work, and/or unable to perform household duties (7-9). As a result, PTS causes major impairment of quality of life (QOL) – patients with PTS have poorer physical functioning, social functioning, general health, and health perceptions; and more severe role limitations (7,10-12). Furthermore, PTS has been estimated to cause ≥ 12% of the new U.S. cases of chronic venous disease (>150,000 patients, direct medical cost $261 million) and venous ulcer (>20,000 patients, direct medical cost $153 million) that occur yearly (13). In a recent study of DVT complications following hip replacement surgery, the per-patient cost of severe PTS was $3817 in the first year and $1677 in subsequent years (14). As venous ulcers recur frequently and are estimated to cause 2 million workdays to be lost yearly, leading to substantial indirect costs, these figures probably underestimate the total economic burden imposed by PTS upon the U.S. healthcare system (15-18). Hence, the disease burden of PTS is of major importance to DVT patients and society at large.

1.2 Importance of Rapid Thrombus Clearance in Reducing the Risk of Developing PTS

1.2.1 Pathogenesis of PTS

The continued presence of thrombus within the deep venous system during the initial weeks and months after a DVT episode is believed to lead to PTS by two pathways: First, residual thrombus physically blocks venous blood flow (obstruction). Second, thrombosis leads to valvular reflux (backwards flow) in the thrombosed deep veins (via an inflammatory reaction which damages the venous valves), and in uninvolved distal deep veins and superficial collaterals (due to compensatory dilatation which separates the valve leaflets) (19,20). The presence of obstruction and/or valvular reflux produces elevated venous pressures when the patient walks or stands upright (“ambulatory venous hypertension”) and leads to edema, tissue hypoxia and injury, progressive calf pump dysfunction, subcutaneous fibrosis, and skin ulceration (21-26). It is therefore logical that rapid elimination of venous thrombus and restoration of unobstructed venous flow (i.e., an “open vein”) should prevent valvular reflux, venous obstruction, and ambulatory venous hypertension, and thereby prevent clinical PTS.

1.2.2 Spontaneous Thrombus Clearance and Development of PTS

Proof-of-concept for this “Open Vein Hypothesis” is provided by several studies of DVT patients treated with standard anticoagulant therapy: **(A)** In a 1993 Duplex ultrasound study of 113 acute DVT patients, Meissner et al found that venous segments that developed valvular reflux had longer (2.3 – 7.3 times) endogenous clot clearance times than segments that did not ($p < 0.04$) (27). **(B)** In 1995, Meissner et al found that valvular reflux developed much less frequently in veins that remained free from DVT propagation or re-thrombosis (26-35% vs 61-80%, $p < 0.005$, $n = 204$) (28). **(C)** In a 2001 study by O’Shaughnessy et al, valvular reflux developed much less frequently in vein segments showing rapid clot clearance (15% vs 70%, $n = 63$) (29). **(D)** In 2004, Prandoni et al found that PTS developed more frequently in proximal DVT patients who had residual venous thrombus or popliteal valvular reflux at 6-month follow-up ($n = 180$, 47% vs 23%, $p < 0.01$) (26). Hence, even in DVT patients treated with standard medical anticoagulant therapy alone, rapid clot clearance correlates with a reduced risk of developing PTS.

1.3 Limitations of Standard DVT Therapy

Standard medical therapy for proximal DVT patients consists of the use of anticoagulant drugs (30). Typically, initial treatment with heparin (subcutaneous injections of a low molecular weight heparin (LMWH) or intravenous administration of unfractionated heparin (UFH)) is given for 5 days, overlapped with oral warfarin (a Vitamin K antagonist) which is continued for at least 3 months. This form of therapy is highly effective in preventing pulmonary embolism (PE). However, anticoagulant drugs do not actively eliminate thrombus. Instead, they rely upon the body’s endogenous fibrinolytic system to clear thrombus but this process has major limitations: a) it can be overridden by a patient’s underlying tendency toward DVT propagation or recurrence (1,3,26,28); and b) the process is often incomplete or too slow to prevent permanent valvular damage from occurring (27,29). As a consequence, PTS occurs frequently (25-50%) in anticoagulated DVT patients (1-5). Although daily use of elastic compression stockings (ECS) reduced PTS rates in three European single-center trials (3,4,31), PTS still occurred in 25-46% of patients who received both anticoagulation and ECS in these studies. Hence, even optimal standard DVT therapy does not prevent PTS in a large proportion of cases.

1.4 Ability of Systemic DVT Thrombolysis Using Streptokinase to Reduce PTS

Systemic DVT thrombolysis refers to venous thrombus dissolution using a fibrinolytic drug administered via an intravenous line distant from the affected limb. Systemic DVT thrombolysis using streptokinase, a first-generation fibrinolytic drug, was evaluated in a number of randomized trials (32). Overall, > 50% clot lysis (by quantitative analysis of venograms) was

achieved more frequently in patients treated with streptokinase than in patients treated with heparin alone (62% vs 17%, $p < 0.0001$) in these studies. In 1979, Elliot et al found that PTS developed less frequently in acute DVT patients treated with streptokinase compared with heparin alone after a mean of 19 months follow-up (35% vs 92%, n = 51) (33). In 1982, Arnesen et al found that venographic obstruction (56% vs 100%) and PTS (24% vs 67%) were less frequent in patients treated with streptokinase compared with anticoagulation alone at a mean of 6.5 years follow-up ($p < 0.01$, n = 42) (34). However, bleeding complications were much more frequent in patients treated with streptokinase. For this reason, although streptokinase did receive FDA approval for DVT, a NIH Consensus Panel later recommended against its use. Still, the streptokinase trials provide important proof-of-concept support for the ability of fibrinolytic therapy to eliminate venous thrombus and prevent PTS in acute proximal DVT.

1.5 Recombinant Tissue Plasminogen Activator (rt-PA) for Systemic DVT Thrombolysis

1.5.1 Background of rt-PA

Activase® (rt-PA, Alteplase, the Study Drug) is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids, and is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. The manufacturing process involves secretion of the enzyme alteplase into the culture medium by an established mammalian cell line (Chinese Hamster Ovary cells) into which the cDNA for alteplase has been genetically inserted. Fermentation is carried out in a nutrient medium containing the antibiotic gentamicin sulfate, 100 mg/L. The presence of the antibiotic is not detectable in the final product. Activase® is commercially available as a lyophilized powder for reconstitution in 2-mg, 50-mg, and 100-mg vials. In this study, the 50-mg Activase® vials will be used. Activase® is indicated for use in acute myocardial infarction, acute non-hemorrhagic stroke, and acute massive PE in adults.

1.5.2 Systemic DVT Thrombolysis with rt-PA

rt-PA is a thrombolytic drug that has the property of fibrin-enhanced conversion of plasminogen to plasmin, an active lytic enzyme which degrades fibrin to soluble peptides. rt-PA produces limited conversion of plasminogen in the absence of fibrin and is therefore believed to preferentially bind to thrombus-adherent fibrin. Theoretical advantages of rt-PA over previous thrombolytic drugs are its relatively short half-life and lack of allergenicity. The ability of systemically-administered rt-PA to lyse human DVT is supported by the following indirect (A) and direct (B and C) evidence: **(A)** The established ability of rt-PA to lyse human PE, which represents migrated DVT (35-41); **(B)** In a 1990 study of 59 proximal DVT patients, Turpie et al

found that a 4-hour systemic rt-PA infusion (0.5 mg/kg) achieved ≥ 50% clot lysis more often than heparin alone (58% versus 0%, p = 0.002), with a trend towards reduced PTS in patients who had ≥ 50% clot lysis (25% vs 56%, p = 0.07) (42). **(C)** In a 1990 multicenter randomized trial of 64 proximal DVT patients, Goldhaber et al found > 50% clot lysis to be more frequent in patients treated with rt-PA (0.05 mg/kg/hr infused for up to 24 hours, maximum dose 150mg) than in patients treated with heparin alone (29% vs 0%, p = 0.04) (43). In this study, > 50% clot lysis was far more frequent in patients with non-occlusive thrombi rather than occlusive thrombi (59% vs 14%, p < 0.005), supporting the concept that inadequate access of rt-PA to its target sites within the thrombus may have contributed to its limited effectiveness (44). These studies showed that rt-PA is biologically active in lysing human DVT but also strongly suggest that the systemic administration route may not reliably achieve a therapeutic rt-PA concentration at its target sites within the thrombus, resulting in only modest (29-58%) clot removal efficacy.

1.5.3 Bleeding Complications with Systemically-Administered rt-PA

The bleeding complications observed in studies of systemic rt-PA infusion for the treatment of venous thromboembolism (VTE) are summarized here: **(A)** In the two randomized controlled trials of rt-PA infusion for proximal DVT noted in the preceding section (n = 123), there was one non-fatal intracranial bleed (42,43). Two patients had extracranial bleeding (one subcutaneous ecchymosis and one hemarthrosis which occurred 10 days after hip surgery). **(B)** In a study of 47 patients with PE who were treated with intravenous rt-PA infusion (50mg over 2 hours), there were two non-fatal major bleeds: one hemopericardium in a patient who had undergone coronary bypass surgery 8 days before, and one bleed from a pelvic tumor which required surgical therapy (35,36). **(C)** In a randomized controlled trial, 45 patients with acute PE were randomized to receive intravenous infusion of either rt-PA (100mg as a continuous infusion over 2 hours) or urokinase (2000 units/lb/hr bolus followed by 2000 units/lb/hr for 24 hours). Of the 22 patients receiving rt-PA, there were no intracranial bleeds but five patients required transfusions for bleeding (37). **(D)** In a 1988 pilot trial, 34 patients with massive PE were randomized to receive rt-PA at 50mg over 2 hours by either intravenous infusion or pulmonary arterial infusion. There were four major non-fatal bleeds, all in patients who had undergone recent surgery (45). **(E)** In a multicenter randomized controlled trial, 87 patients with PE were randomized to receive intravenous infusion of either rt-PA (100mg over 2 hours) or urokinase (intravenous infusion of 3 million units over 2 hours with the first 1 million units given over 10 minutes). Of the 44 patients receiving rt-PA, there were two intracranial bleeds (one fatal) (38). **(F)** In a multicenter randomized controlled trial, 87 patients with PE received rt-PA infusions at either 0.6 mg/kg over 15 minutes (maximum 50mg) or 100mg over 2 hours (40). There were 14 major bleeding

complications, including two fatal bleeds in the 15-minute infusion group (one intracranial bleed and one hemopericardium) and none in the 2-hour infusion group. **(G)** In two studies evaluating risk factors for bleeding with rt-PA infusions for PE, advanced age and severe hypertension were associated with increased bleeding complications (46,47). **(H)** In a 2002 multicenter randomized trial of patients with submassive PE who received intravenous rt- PA infusion (100 mg over 2 hours) + heparin or heparin alone, there were no intracranial or fatal bleeds in the 118 rt-PA recipients (41). Together, these studies show that systemic rt-PA infusions are associated with a small but significant risk of serious bleeding in VTE patients.

1.6 Catheter-Directed Intrathrombus Thrombolysis (CDT) for DVT

Catheter-directed intrathrombus thrombolysis (CDT) refers to thrombus removal by administration of a fibrinolytic drug directly into the deep vein thrombus via a device/catheter which is embedded within the thrombus using imaging guidance (48). CDT is provided as an adjunct to standard anticoagulant therapy during the initial treatment of acute proximal DVT. CDT is a minimally-invasive procedure that is performed with the patient under conscious sedation. Unlike anticoagulant therapy, CDT provides rapid thrombus removal and restoration of unobstructed deep venous flow in > 80% of patients with acute proximal DVT and is therefore expected to prevent valvular reflux, venous obstruction, and PTS (49). Unlike surgical venous thrombectomy, CDT does not require general anesthesia, open surgery, or a prolonged recovery period. CDT should be more effective than systemic DVT thrombolysis since it delivers the fibrinolytic drug directly into the thrombus and thereby achieves higher local drug concentrations (50). By increasing lytic efficacy, CDT is expected to enable successful DVT therapy with a lower dose of the fibrinolytic drug, which should reduce bleeding complications.

1.6.1 CDT Studies in Proximal DVT Using Streptokinase and Urokinase

The ability of CDT to rapidly remove venous thrombus and prevent PTS in proximal DVT patients is supported by several studies, but each had significant methodological limitations: **(A)** In a multicenter registry of 473 DVT patients who received CDT using urokinase (mean 7.8 million units), ≥ 50% clot lysis was observed in 83% of patients and was more frequent in patients with acute DVT (87% versus 68% for chronic DVT, $p < 0.01$) or first-episode DVT (86% versus 74% for recurrent DVT, $p < 0.003$) (49). Successful clot lysis was equally frequent in patients with acute iliofemoral DVT versus acute isolated femoropopliteal DVT. In a follow-up study, Comerota et al analyzed data from 68 CDT-treated acute iliofemoral DVT patients in this registry and found that they had fewer PTS symptoms ($p = 0.006$), better physical functioning ($p = 0.046$), less stigma of chronic venous insufficiency ($p = 0.033$), and less health distress ($p =$

0.022) at a mean follow-up of 16 months than 30 patients who were treated with anticoagulation alone (51). However, these studies were not randomized trials and the quality of life comparison was limited by marked age differences in the two cohorts. **(B)** In 2001, AbuRahma et al described a prospective study in which 51 acute iliofemoral DVT patients were permitted to choose to receive adjunctive CDT (with urokinase or rt-PA) + anticoagulation or anticoagulation alone. The patients treated with CDT had more frequent venous patency at 6 months (83% versus 24%, P < 0.0001) and absence of symptoms at 5 years (78% versus 30%, p = 0.0015) (52). However, this study was limited by non-randomized design, performance in a single center, and small sample size. **(C)** In 2002, Elsharawy et al described a single-center Egyptian randomized trial comparing adjunctive CDT (with streptokinase) versus anticoagulation alone in 35 patients with acute iliofemoral DVT. At 6 months, patients treated with CDT had a higher rate of normal venous function (72% versus 12%, p < 0.001) and less valvular reflux (11% versus 41%, p = 0.04) as assessed by Duplex ultrasound, photo plethysmography, and air plethysmography (53). However, this study was limited by small sample size and performance in a single center, and did not evaluate clinically-meaningful outcomes such as PTS and QOL.

1.6.2 Early CDT Studies with Recombinant t-PA

Observational studies have described the use of rt-PA, given by catheter-directed intrathrombus infusion, to successfully lyse proximal DVT (54-59). In early experiences, weight-based or non-weight-based rt-PA infusion regimens of 2-5 mg/hr were used. However, anecdotal reports from physicians using these rt-PA regimens suggested that bleeding complications were more frequent compared with the previous urokinase experience. In an early study in which intrathrombus rt-PA was administered to 24 proximal DVT patients at 3 mg/hr, major bleeding was observed in 25% of patients (54). In a study of 35 patients who received intrathrombus rt-PA infusions at up to 0.04 mg/kg/hr for peripheral arterial occlusions, major bleeding requiring transfusion occurred in 22% of patients (60). In a 653-patient registry of patients treated with intrathrombus rt-PA infusions for arterial and venous thrombolysis, the rates of major (22%) and intracranial (2.8%) bleeding were substantial (55). For these reasons, an Advisory Panel convened by the Society of Interventional Radiology (SIR) recommended against the use of rt-PA infusions exceeding 2 mg/hr (61,62).

1.6.3 CDT Studies with "Low-Dose" Recombinant t-PA

The use of "low-dose" ($\leq$ 2 mg/hr) intrathrombus rt-PA infusions to treat proximal DVT has been described in several studies: **(A)** In a 2001 study by Shortell et al, low-dose rt-PA infusions (2 mg/hr with a maximum dose of 100mg) via CDT provided > 50% clot lysis as often (77% versus 81%, p = NS) and faster (30 hours versus 43 hours) than urokinase (240,000 units/hr for 4 hours

then 120,000 units/hr) in acute DVT patients (n = 31) (56). **(B)** In 2003, Sugimoto et al found that catheter-directed infusions of low-dose rt-PA (1 mg/hr) and urokinase (120,000 units/hr) had equal efficacy (≥ 50% clot lysis in 88% versus 83%) and safety (major bleeds 4% in both groups) for treatment of DVT (n = 54) (57). rt-PA infusions were faster (24 hours versus 33 hours, p = 0.011) and less costly ($418 versus $6032, p < 0.0001). **(C)** In 2004, Grunwald et al found rates of clot lysis (97% for rt-PA) and complications (3% for rt-PA) to be comparable for rt-PA (0.5-1.0 mg/hr), urokinase (mean dose 113,000 units/hr), and reteplase (0.5-1.0 unit/hr) in a non-randomized study of 82 DVT patients (58). Drug costs were lower for rt-PA ($488) than reteplase ($1787) or urokinase ($6577) (p < 0.05). Based upon these studies, the SIR subsequently recommended rt-PA dosing of 0.5 - 1.0 mg/hr in its 2006 quality improvement guidelines for endovascular DVT interventions (63). **(D)** In 2008, Kim et al reported the use of intrathrombus rt-PA infusions to treat 178 patients with DVT (59). Successful (> 50%) clot lysis was observed in 92% of treated limbs, with major bleeding in 4% of patients. Bleeding complications were more common in patients ≥ 70 years of age. Notably, there was no intracranial or fatal bleeding in these four studies. Hence, low-dose rt-PA infusions via CDT have been reasonably safe and have produced clot lysis at rates (81-97%) that have far exceeded those of systemic rt-PA delivery.

1.6.4 Limitations of Early CDT Methods

The above studies support rt-PA's ability to remove acute venous thrombus, resulting in CDT's acceptance as a "salvage" treatment for a small minority of patients with particularly severe DVT manifestations. However, these studies also illustrate why the routine first-line use of CDT in proximal DVT is controversial. In the above studies, monitoring of the prolonged (30-48 hours) infusions needed to achieve clot lysis required intensive care unit (ICU) stays of 1-3 days – the use of these precious hospital resources is a major barrier to routine use of CDT. Also, it has been hypothesized that the prolonged systemic exposure to rt-PA delivered via traditional CDT may have increased the risk of major bleeding (11% in the urokinase registry, 2-5% in studies of low-dose rt-PA), including the rare catastrophic bleeding events (49). Given the absence of a multicenter randomized trial proving that CDT provides a long-term health benefit by preventing PTS, CDT is not recommended for routine treatment of proximal DVT (30). These concerns have prompted the development of methods to minimize systemic exposure to rt-PA during CDT.

1.6.5 Contemporary Performance of CDT

In current practice, most endovascular physicians utilize catheter-based percutaneous mechanical thrombectomy (PMT) devices to deliver and/or optimally disperse the fibrinolytic drug within the clot. These **Pharmacomechanical CDT (PCDT)** methods appear to accelerate clot lysis and

reduce the rt-PA dose compared with earlier CDT methods, and are therefore believed to optimize safety and efficiency. Recently, PCDT using the Trellis Peripheral Infusion System (Bacchus Vascular, Santa Clara, CA) and the Angiojet Rheolytic Thrombectomy System (Possis Medical, Minneapolis, MN) has been shown to enable **single-session DVT treatment** without the need for prolonged infusions or ICU admission. While there are no randomized trials, the Table below lists recent case series and cohort studies in which single-session PCDT was used for proximal DVT:

Study	≥ 50% Clot Lysis	Device	Single-Session	Major Bleeds
Kasirajan 2003 (64)	75%	Trellis	85%	0%
Spencer 2003 (65)	95%	Trellis	50%	5%
McNamara 2003 (66)	100%	Trellis	100%	0%
Bush 2004 (67)	74%	Angiojet	65%	0%
Lin 2006 (68)	81%	Angiojet	75%	4%
Cynamon 2006 (69)	100%	Angiojet	79%	8%
Garcia 2007 (70)	82%	Angiojet	57%	3%
O'Sullivan 2007 (71)	96%	Trellis	100%	0%
Hilleman 2008 (72)	93%	Trellis	80%	0%

Regarding costs, Lin et al found PCDT to reduce ICU stay (0.6 days vs 2.4 days, $p < 0.04$) and hospital costs ($47,742 vs $85,301 per patient, $p < 0.01$) compared to stand-alone CDT (68). Hilleman et al found reduced drug/device costs ($3697 vs $5473, $p = 0.03$) for Trellis PCDT in a comparison of data from a manufacturer's registry with previous studies of stand-alone CDT (72).

1.6.6 Current Status of PCDT

There remains significant uncertainty and clinical equipoise among physicians regarding the best initial treatment for proximal DVT. The American College of Chest Physicians (ACCP) has recommended against use of PCDT for DVT other than in exceptional circumstances, and only recently acknowledged its potential utility in patients with highly symptomatic DVT that is not causing acute limb threat (30,73). In contrast, the SIR has endorsed PCDT for ambulatory patients with extensive acute proximal DVT, low bleeding risk, and long life-expectancy (74). The strong possibility of a meaningful benefit to patients, the potential risks and costs of PCDT, and the lack of physician consensus on the treatment of proximal DVT provide a compelling scientific and ethical rationale for a multicenter randomized trial to evaluate clinical outcomes with PCDT.

1.6.7 The ATTRACT Trial

To determine if PCDT should be routinely used to treat proximal DVT, we plan to perform a

multicenter randomized clinical trial (the **A**cute Venous **T**hrombosis: **T**hrombus **R**emoval with **A**djunctive **C**atheter-Directed **T**hrombolysis [**ATTRACT**] Trial) to establish whether PCDT prevents PTS and improves health-related QOL with acceptable safety and costs. If so, this finding is expected to catalyze a fundamental change in DVT practice towards routine, first-line use of PCDT. If PCDT proves ineffective or insufficiently safe, this finding will reduce or eliminate the use of a potentially risky and expensive procedure. The ATTRACT Steering Committee includes accomplished DVT researchers who have specialized expertise with PCDT, the conduct of multicenter DVT treatment trials, and the evaluation of PTS. The need for this study, which is being funded by the National Heart Lung and Blood Institute (NHLBI) under grants 1U01088476-01A1 (Clinical Coordinating Center) and 1U01HL088118-01A1 (Data Coordinating Center), has been endorsed by multidisciplinary panels of the SIR Foundation (75), the American Venous Forum (76), and the panelists at the May 2006 Surgeon General's DVT Workshop. The ATTRACT Trial has been specifically endorsed by the SIR Foundation, the American Venous Forum, and the American College of Phlebology. Hence, there is broad consensus that ATTRACT addresses a research question of major importance to patients, physicians, and the U.S. healthcare system.

1.7 Summary of Rationale for the Proposed Study

The rationale for performing the ATTRACT Trial is based upon (a) the major burden of PTS on DVT patients and the U.S. healthcare system; (b) the association between rapid clot lysis and prevention of PTS; (c) the proven ability of rt-PA (the Study Drug) to dissolve venous thrombus in proximal DVT; (d) recent advances in PCDT methods which may lower bleeding risk; and (e) the major clinical controversy on whether PCDT should be routinely used for first-line DVT therapy.

2 STUDY OBJECTIVES

2.1 Primary Objective

In symptomatic patients with acute proximal DVT, to determine if initial adjunctive use of PCDT (using rt-PA) with optimal standard DVT therapy reduces the occurrence of the Post-Thrombotic Syndrome during 24 months of follow-up compared with optimal standard DVT therapy alone.

2.2 Secondary Objectives

- To compare between the two treatment arms: the resolution of acute DVT symptoms; rates of major bleeding, symptomatic PE, recurrent venous thromboembolism, and death; venous disease-specific and general QOL; and cost-effectiveness;
- To identify pre-treatment predictors of heightened therapeutic response to PCDT via correlation of PTS scores and QOL change scores with demographic variables, DVT risk

factors, symptom duration, and anatomic thrombus extent; and

- To determine the anatomic/physiologic conditions needed to prevent PTS via correlation of PTS scores and QOL change scores with post-treatment thrombus burden, recurrent DVT, and valvular reflux.

3 STUDY DESIGN

This is an NIH-funded, Phase III, multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial. 692 subjects with symptomatic proximal DVT that involves the iliac, common femoral, and/or femoral vein will be randomized in a 1:1 ratio to receive either adjunctive PCDT (with rt-PA) + standard DVT therapy or standard DVT therapy alone. Subjects will be enrolled over 4.5 years in 30-60 U.S. Clinical Centers, and followed for 24 months. The study will take 6.5 years to complete. **Appendix 1** outlines the trial's organizational structure.

4 SUBJECT SELECTION

4.1 Subject Identification and Index Leg Designation

At the Clinical Centers, subjects will be identified by Vascular Ultrasound Laboratory personnel who diagnose DVT, by pharmacy personnel who dispense anticoagulant drugs, by Emergency Department physicians and hospital physicians who treat DVT patients, and by the ATTRACT investigator physicians. Subjects may also be referred from regional facilities.

For patients who present with bilateral DVT, the investigator must designate which lower extremity will be considered the "index leg" to be used in the study outcome analyses. In general, the index leg should be the leg that would be most likely to prompt the use of PCDT in clinical practice. Designation of the index leg must be documented prior to randomization.

4.2 Inclusion Criterion

Symptomatic proximal DVT involving the iliac, common femoral, and/or femoral vein.

4.3 Exclusion Criteria

Subjects meeting any of these criteria will be excluded (all times are relative to screening date):

1. Age less than 16 years or greater than 75 years.
2. Symptom duration > 14 days for the DVT episode in the index leg (i.e., non-acute DVT).
3. In the index leg: established PTS, or previous symptomatic DVT within the last 2 years.
4. In the contralateral (non-index) leg: symptomatic acute DVT a) involving the iliac and/or common femoral vein; or b) for which thrombolysis is planned as part of initial therapy.

5. Limb-threatening circulatory compromise.
6. PE with hemodynamic compromise (i.e., hypotension).
7. Inability to tolerate PCDT procedure due to severe dyspnea or acute systemic illness.
8. Allergy, hypersensitivity, or thrombocytopenia from heparin, rt-PA, or iodinated contrast, except for mild-moderate contrast allergies for which steroid pre-medication can be used.
9. Hemoglobin < 9.0 mg/dl, INR > 1.6 before warfarin was started, or platelets < 100,000/ml.
10. Moderate renal impairment in diabetic patients (estimated GFR < 60 ml/min) or severe renal impairment in non-diabetic patients (estimated GFR < 30 ml/min).
11. Active bleeding, recent (< 3 mo) GI bleeding, severe liver dysfunction, bleeding diathesis.
12. Recent (< 3 mo) internal eye surgery or hemorrhagic retinopathy; recent (< 10 days) major surgery, cataract surgery, trauma, CPR, obstetrical delivery, or other invasive procedure.
13. History of stroke or intracranial/intraspinal bleed, tumor, vascular malformation, aneurysm.
14. Active cancer (metastatic, progressive, or treated within the last 6 months). Exception: patients with non-melanoma primary skin cancers are eligible to participate in the study.
15. Severe hypertension on repeated readings (systolic > 180mmHg or diastolic > 105mmHg).
16. Pregnant (positive pregnancy test, women of childbearing potential must be tested).
17. Recently (<1 mo) had thrombolysis or is participating in another investigational drug study.
18. Use of a thienopryridine antiplatelet drug (except clopidogrel) in the last 5 days.
19. Life expectancy < 2 years or chronic non-ambulatory status.
20. Inability to provide informed consent or to comply with study assessments (e.g. due to cognitive impairment or geographic distance).

4.4 Screening Procedures

When a potential subject is identified, the following steps should be taken:

1. The investigator should confirm that proximal DVT with involvement of the iliac, common femoral, and/or femoral vein has been objectively diagnosed, as indicated by:
   a) on ultrasound, a non-compressible or incompletely compressible venous segment in the common femoral and/or femoral vein (77); or
   b) on venography or contrast-enhanced CT scan, abrupt cutoff of or a constant intraluminal filling defect in the iliac, common femoral, and/or femoral vein (78).

2. A study staff member should screen the medical history and laboratory studies to confirm that the patient may be eligible – if not, the reason(s) should be recorded in a screening log. When a potentially eligible patient is identified, a member of the research team should contact the patient's physician to determine whether he/she is willing to enroll the patient. If so, the patient's physician should approach the patient first to determine if he/she is willing to be contacted by the research team. If the patient's physician or a research team member believes that the patient is cognitively impaired or otherwise unable to provide informed consent, the patient should not be invited to participate in the study. All subjects should be able to understand the nature of the research and their participation, appreciate the consequences of participation in the study, show the ability to consider alternatives including the option of non-participation, and show the ability to make a reasoned choice.
3. If the patient has a history of a mild-moderate allergic reaction to iodinated contrast, the patient's physician should be asked if the patient may be treated with PCDT under steroid pre-medication, if he/she were randomized to PCDT. If yes, the patient may be enrolled. Patients who have had any allergic reaction to iodinated contrast which occurred while receiving steroids, or who cannot receive steroid pre-medication, should be excluded.
4. The study staff member should explain the study to the patient in a non-coercive manner and provide him/her with a Study Informed Consent Form to review, sign, and date. A copy should be provided to the patient and the original retained by the Clinical Center. For subjects who are minors, one parent's written consent and the child's written assent are required. However, permission should be sought from both parents whenever possible. For subjects who are not fluent in English, the informed consent process should be conducted in the subject's native language, utilizing a qualified translator when appropriate.
5. Subjects who agree to participate must undergo:
    - A history, physical exam including vital signs, and measurement of height and weight.
    - The following tests: complete blood count with platelets, PT/INR, creatinine, and a blood or urine pregnancy test (in women of childbearing potential). To avoid unnecessary venipuncture, the results of laboratory tests performed within 3 days prior to randomization may be used. The results should be reviewed – if the hemoglobin is < 9.0 mg/dl, the platelets are < 100,000/ml, or the pregnancy test is positive, the patient should be excluded unless the tests are repeated and found to be in the eligible range.

- The estimated glomerular filtration rate (eGFR) should be calculated using the Modification of Diet in Renal Disease (MDRD) Study formula (79,80). Non-diabetics with an eGFR between 30-60 ml/min should be excluded if they cannot receive pre-procedure hydration prior to PCDT (e.g., due to severe congestive heart failure).
- Patients with an INR > 1.6 on studies obtained prior to initiation of warfarin must be excluded. Patients with an INR > 1.6 may be enrolled provided that administration of Vitamin K is expected to bring the INR down to 1.6 or less (i.e., if randomized to PCDT).

4.5 Baseline Evaluation

After eligibility is established and informed consent is obtained, but before randomization, subjects should undergo the following baseline assessments (see Section 8 for details):

- Self-completion of QOL questionnaires (SF-36v2, VEINES);
- Self-rating of baseline leg pain (7-point Likert scale) (both legs);
- Calf circumference measurement (both legs);
- Administration of Villalta's PTS Scale (both legs); and
- Venous Duplex ultrasound of the index leg. A previous ultrasound may be used if it was performed within 5 days prior to randomization, provided that its scope was adequate (i.e. compression of the proximal veins of the leg was clearly documented, enabling entry of this information on the Compression Ultrasound Case Report Form).
- Examination of the contralateral lower extremity is encouraged but optional; if performed, the findings should also be entered on the Compression Ultrasound Case Report Form.

5 RANDOMIZATION

5.1 Timing of Randomization

In general, the patient should be randomized as soon as possible after the baseline evaluation is completed. If it is expected that there would be a substantial delay (> 24 hours) between randomization and when PCDT could actually be performed if the patient was allocated to PCDT, randomization may be deferred until PCDT can be performed within 24 hours. In Experimental Arm subjects, PCDT should be performed within 3 days after randomization.

5.2 Stratification

Prior to randomization, subjects will be stratified on two factors:

(1) Highest anatomic extent of DVT: iliofemoral DVT (DVT that involves the common femoral vein and/or iliac vein) versus isolated femoropopliteal DVT (femoral DVT that does not

involve the common femoral vein or iliac vein), as this may influence PTS rates (11,49,81);

(2) Clinical Center: to reduce the potential for confounding due to between-Center differences in enrolled subjects or their general management (82).

5.3 Central Automated Randomization

Clinical Center staff will access the web-based Interactive Registration/Randomization System (IRIS) at the Data Coordinating Center (DCC) that leads the staff through a series of questions related to the patient's eligibility status and stratification category, then provides treatment group allocation. Each Center will be given a unique study and Center-specific authorization code to access IRIS. The complete randomization sequence will be computer-generated by a DCC statistician who is not involved with the ATTRACT Trial before the first patient is randomized.

6 TREATMENT DESCRIPTION

In this section, a brief description of the treatments that will be administered to ATTRACT subjects is provided. The detailed, step-by-step description of how the treatments should be administered to the study subjects is provided in Section 7 (Treatment Procedures).

6.1 Optimal Standard DVT Therapy (All Subjects)

All subjects (in the Experimental and Control Arms) will receive standard anticoagulant therapy for DVT (30). In each Clinical Center, this will be supervised by a board-certified physician who is experienced in managing anticoagulant therapy in DVT and who has been credentialed for this study by an expert Medical Therapy Committee (Section 19.3.4).

6.1.1 Initial Anticoagulant Therapy

All subjects in both treatment arms will receive initial anticoagulant therapy for at least 5 days. One of the regimens below should be used, as selected by the medical co-investigator (30). The LMWH doses may be reduced in subjects with renal impairment, per the medical co-investigator.

a) **Enoxaparin** by subcutaneous injection twice-daily at 1 mg/kg, or once-daily at 1.5 mg/kg.
b) **Dalteparin** by subcutaneous injection once daily at 200 IU/kg, or twice-daily at 100 IU/kg.
c) **Tinzaparin** by subcutaneous injection once daily at 175 anti-Xa IU/kg.
d) **Intravenous UFH**. An initial intravenous bolus of 80 units/kg (maximum allowable dose 5000 units) will be given to subjects who are not already anticoagulated. An intravenous UFH infusion will be initiated at 18 units/kg/hour or at a rate which has previously been shown to correspond to a PTT level within the therapeutic range in that subject. UFH dose

adjustments will be made per institutional nomogram, using a target PTT that corresponds to plasma heparin levels of 0.3 – 0.7 IU/ml anti-Xa activity in that institution. Prior to start-up, each Clinical Center will submit these items for approval by the Medical Therapy Committee: (a) Clinical Laboratory Improvement Amendment (CLIA) & College of American Pathologists (CAP) certifications; and (b) nomogram for PTT monitoring and UFH dose adjustments. To accommodate differences between hospital anticoagulation policies, minor variances from the above parameters may be allowed with approval from the Medical Therapy Committee.

The use of heparin assay measurements of anti-Xa activity (instead of PTT values) to monitor heparin therapy and guide dose adjustments is allowed at sites where this is routine practice and where the heparin assay is always available. At such sites, an anti-Xa activity level should be obtained and documented whenever a PTT value is required by the protocol.

The use of non-heparin drug regimens for initial anticoagulant therapy (i.e. during the first 5-7 days after enrollment) is discouraged without a strong justification and approval by the medical co-investigator and study Principal Investigator.

6.1.2 Long-Term Anticoagulant Therapy with Warfarin

All subjects in both treatment arms will receive long-term anticoagulant therapy. Oral warfarin should generally be used at an initial dose of 2.5 - 10 mg/day, with the specific dose selected by the medical co- investigator. The recommended intensity (target INR 2.0 to 3.0) and duration of warfarin therapy will be the same for subjects in the two treatment arms. Warfarin will be given for a minimum of 3 months (30). In subjects with DVT in association with a major reversible risk factor such as surgery or plaster cast immobilization within the preceding 6 weeks, warfarin will usually be stopped after 3 months. In subjects with unprovoked DVT, indefinite anticoagulant therapy is generally recommended. However, subjects with unprovoked DVT may stop anticoagulant therapy after 3 to 6 months, or subsequently, if there are risk factors for bleeding, difficulties with anticoagulant control, or if it is the subject's preference to stop therapy. The actual duration of anticoagulant therapy given and the percent of time spent in the therapeutic range will be recorded and compared between the two treatment groups. During follow-up, subjects may be treated with alternative anticoagulant regimens at the medical co-investigator's judgment, using the above guidelines for the duration of anticoagulant therapy. Prior to start-up, each Clinical Center will submit its warfarin monitoring plan to the Medical Therapy Committee for review/approval.

Whenever possible, the medical co-investigator should assume primary responsibility for the

subject's long-term DVT care. However, for subjects who live far from the Clinical Center, warfarin monitoring may be provided by a local physician. However, in these instances, the medical co-investigator is still responsible to communicate with the local physician to ensure that the DVT care being provided is appropriate and consistent with this protocol. The medical co-investigator is responsible for obtaining records of INR laboratory studies during follow-up, and must be notified of any changes to anticoagulant therapy and any planned endovascular DVT treatment procedures to ensure that they are consistent with this protocol. Any such changes to therapy must be documented on the Anticoagulation Change Case Report Form or the Late Endovascular Procedure Case Report Form. Importantly, the subject must still return to the Clinical Center for the scheduled follow-up visits and outcome assessments.

6.1.3 Elastic Compression Stockings (ECS)

All subjects will be given sized-to-fit, knee-high, 30-40 mmHg ECS (donated by BSN-Jobst) at the 10-day follow-up visit. A new pair will be provided every 6 months. At each follow-up visit, ECS use will be reinforced in a standardized way and compliance will be recorded (3,31).

6.1.4 Inferior Vena Cava Filters

IVC filters will not be routinely placed in ATTRACT subjects. Per standard medical practice, IVC filters (any FDA-approved device) may be placed in subjects who develop contraindications to anticoagulant therapy during the study and in subjects who fail anticoagulation (defined as symptomatic PE despite therapeutic-level anticoagulation). The use of alternative anticoagulant regimens (e.g. LMWH) should be considered before placing IVC filters in subjects with DVT progression despite therapeutic-level anticoagulation with warfarin. In subjects randomized to PCDT, pre-procedure placement and post-procedure removal of FDA-approved, retrievable IVC filters for peri-procedure PE prevention will be allowed in certain situations (see Section 6.2.5).

6.2 Pharmacomechanical Catheter-Directed Thrombolysis (Experimental Arm Only)

Subjects randomized to the Experimental Arm will receive initial adjunctive PCDT in addition to the optimal standard DVT therapy outlined in Section 6.1. PCDT will be performed by a board-certified endovascular physician who is experienced with thrombolytic therapy for DVT and who has been credentialed by an expert Interventions Committee (Section 19.3.3).

6.2.1 rt-PA (Activase®, the Study Drug)

6.2.1.1 Drug Formulation and Storage

Activase® is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous

administration after reconstitution with sterile water for injection, USP. Activase® is supplied in 50-mg vials containing vacuum. Activase® should be reconstituted only with sterile water for injection, USP, without preservatives. The resulting preparation is a colorless to pale yellow transparent solution containing Activase® 1 mg/ml at a pH of about 7.3. Activase® should be stored at controlled room temperature ≤ 30 degrees Celsius (86 degrees Farenheit), or under refrigeration at 2-8 degrees Celsius (36-46 degrees Farenheit), per package insert. Activase® should be protected from excessive exposure to light, and should not be used beyond the vial's expiration date. For details, see the Activase® package insert and Investigator's Brochure.

6.2.1.2 Drug Distribution, Labeling, and Accountability

Genentech will supply the Activase® to the Clinical Coordinating Center (CCC) at Washington University. At the CCC, the Activase® will be stored per its package insert in the Washington University Core Laboratory for Clinical Studies, from which it will be distributed to the Clinical Center pharmacies. The Activase® will be clearly labeled as being for research purposes only. At the CCC, a Drug Inventory Log will be kept to track the receipt and distribution of the drug.

An Investigational Drug Accountability Log entry must be completed by the Clinical Center, and faxed to the CCC, each time rt-PA is received, dispensed, or destroyed. Damaged supplies will be replaced by the CCC. All expired or unused rt-PA and empty containers at the Clinical Center or at the CCC will be disposed of per the institution's standard drug destruction procedure. Written documentation of what vials were discarded, and the date, is mandatory.

6.2.2 Overview of Endovascular DVT Treatment Procedures

In clinical practice, endovascular DVT treatment procedures involve 5 distinct "phases" during which multiple component endovascular techniques are commonly employed. The use of the different PCDT techniques and methods is summarized in **Appendices 2 and 3**.

Phase 1 Procedure Initiation (Section 7.3.3) involves obtaining catheter access to the deep venous system and defining the anatomic extent of the thrombus via venography.

Phase 2 Initial PCDT (Section 7.3.4 and **Appendices 4-6**) involves the initial intrathrombus delivery and dispersion of rt-PA with an FDA-approved drug delivery device/catheter.

After Initial PCDT, the measures that must be taken to achieve an open vein and prevent immediate re-thrombosis depend upon the amount and location of residual thrombus and/or venous stenosis, which vary widely among subjects. Hence, for Phases 3 and 4, investigators will be allowed the flexibility to tailor adjunctive therapy, aimed at eliminating residual thrombus and/or venous stenosis, to individual patient circumstances, pursuant to certain guidelines.

Phase 3 Clean-Up of Residual Thrombus (Section 7.3.5) involves the use of adjunctive endovascular techniques that are routinely used by physicians to improve rt-PA delivery to the thrombus and to prevent re-thrombosis by optimizing venous flow.

Phase 4 Treatment of Venous Obstruction (Section 7.3.6) involves standard endovascular treatment for venous obstructive lesions that can cause re-thrombosis if untreated.

Phase 5 Completion of PCDT Procedures (Section 7.3.7) involves completion venography, vascular sheath removal, and transition to subsequent anticoagulant therapy.

In patients with bilateral DVT, the non-index leg may not be treated with PCDT as part of the initial treatment approach. If thrombolysis is later felt to be necessary to treat the DVT in the non-index leg, ATTRACT Study Drug should not be used for the procedure.

6.2.3 Allowed Techniques for Initial PCDT (Intrathrombus Delivery/Dispersion of rt-PA)

Given that (a) physicians have different preferences for which FDA-approved catheter/device to use to deliver and disperse rt-PA into the thrombus, and are likely to achieve their best results using the PCDT method with which they are most comfortable; (b) no single PCDT method has been proven superior to another; and (c) the extent of thrombus may be an important factor in determining the likelihood of success with single-session PCDT, three different PCDT methods will be used in ATTRACT subjects. The primary data analysis will compare all Experimental Arm subjects regardless of which PCDT method was used versus all Control Arm subjects.

The three PCDT techniques are summarized below. As Technique A (Trellis PCDT) and Technique B (AngioJet PCDT) are used with the intent of providing complete DVT thrombolysis in a single procedure session, all five phases of endovascular therapy should be completed during a single procedure session in most of these patients (64-72). In contrast, Technique C (Infusion-First PCDT) is a multi-session technique that begins with a traditional rt-PA infusion via a multisidehole infusion catheter (83). Thrombolytic progress is assessed at subsequent procedure sessions, during which Phases 3-5 of endovascular DVT therapy are completed. Hence, endovascular therapy will require 1-4 procedure sessions over 30 hours (maximum).

6.2.3.1 Technique A (Trellis PCDT)

The Trellis-8 Peripheral Infusion System is a multi-lumen catheter with two compliant balloons (which, when inflated, isolate a treatment zone) near its distal end and multiple infusion sideholes (for intrathrombus rt-PA injection) between the balloons (71,72,84-87). A Dispersion Wire oscillates within the catheter to macerate thrombus and disperse the rt-PA within the isolated zone. Aspiration may then be performed through the catheter to remove the rt-PA.

Initial rt-PA Dose:	1mg rt-PA per 3-4cm thrombus (which is 0.25 to 0.33mg rt-PA per cm thrombus), minimum 4mg
Maximum Allowed rt-PA Dose:	25mg for the first session, 35mg total
Concomitant Heparin:	Therapeutic-level UFH or LMWH
Step-by-step Protocol:	See Section 7 and **Appendix 4**

6.2.3.2 Technique B (AngioJet PCDT)

The AngioJet Rheolytic Thrombectomy System consists of a drive unit/pump, a single-use pump set, and a disposable rheolytic catheter. The system is activated via a foot pedal. The drive unit/pump generates high pressure (10,000 psi) pulsatile saline flow that exits the catheter tip through retrograde-directed jets. This creates a localized low-pressure zone (Bernoulli effect) around the catheter tip to enable clot maceration and evacuation through its effluent lumen. The AngioJet works in an isovolumetric manner – the saline infusion rate is in balance with the evacuation rate of thrombus particulate debris. Two methods may be used to deliver rt-PA via the AngioJet. With the “Powerpulse” method, the effluent lumen is occluded with a closed stopcock, and the AngioJet is used in PowerPulse mode to pulse-spray rt-PA into the thrombus (67-69, 84,85). Alternately, the rt-PA may be dissolved within the saline infusate and this solution infused during use of the AngioJet in aspiration mode (“Rapid Lysis” method) (70).

Initial rt-PA Dose:	1mg rt-PA per 3-4cm thrombus (which is 0.25 to 0.33mg rt-PA per cm thrombus), minimum 4mg
Maximum Allowed rt-PA Dose:	25mg for the first session, 35mg total
Concomitant Heparin:	Therapeutic-level UFH or LMWH
Step-by-step Protocol:	See Section 7 and **Appendix 5**

6.2.3.3 Technique C (Infusion-First PCDT)

A multisidehole infusion catheter will be positioned within the thrombus with its infusion segment spanning the extent of thrombus (56-63). Use of an endhole-only catheter is not permitted. A rt-PA solution will be continuously infused into the thrombus via the catheter. The subject will be monitored in an ICU or stepdown unit and will undergo follow-up venography within 6-24 hours.

Initial rt-PA Infusion:	0.01 mg/kg/hr (maximum 1.0 mg/hr for 30 hours)
Maximum Allowed rt-PA Dose:	35mg total (includes initial infusion & later doses)
Concomitant Heparin:	LMWH or subtherapeutic UFH (6-12 units/kg/hr, maximum dose 1000 units/hr, target PTT less than 2 times control (no minimum PTT)), target anti-Xa activity

level less than 0.5 IU/ml anti-Xa (63,90)

Step-by-step Protocol: See Section 7 and **Appendix 6**

6.2.4 Guidelines for the Choice of Initial PCDT Technique

The following guidelines should be used to select which PCDT method to use in study subjects:

1. Prior to Clinical Center start-up, each Clinical Center must designate **Technique A or B** as the method that will be used in all PCDT Arm subjects at that Center who have good popliteal vein inflow (e.g. the caudal-most extent of the thrombus is more than 3cm above the caudal end of the popliteal vein) **and** no IVC thrombus (68,72). To optimize the CCC's ability to troubleshoot issues relating to all techniques, and to allow the Principal Investigator to remain impartial, the Washington University site (only) will alternate between Techniques A and B at prospectively-defined, 3-month intervals.
2. **Technique C** should be used in subjects with poor popliteal vein inflow (e.g. when the thrombus involves the entire popliteal vein and/or extends into one or more tibial veins), in those found to have thrombus in the IVC (as shown on the pre-PCDT venogram).
3. The endovascular physician may choose to use the Center's designated single-session PCDT method (**Technique A or B**) or infusion-first PCDT (**Technique C**) for all other situations (e.g. if the caudal-most extent of thrombus is within the lower popliteal vein).

6.2.5 Allowed Adjunctive Endovascular Techniques

The following adjunctive endovascular techniques may be used, per the guidelines below, as they are widely used in standard clinical practice to enhance the delivery of rt-PA into the clot or to prevent complications of PCDT (specifically, pulmonary embolism and early re-thrombosis):

1. Retrievable IVC Filters: Retrievable IVC filters are commonly used by endovascular physicians to prevent peri-procedural PE in selected patients undergoing PCDT. In a large prospective registry of proximal DVT patients undergoing infusion CDT (without mechanical thrombectomy), symptomatic PE occurred in only 1.3% (49). Therefore, IVC filter placement is discouraged in patients undergoing Infusion-First PCDT (Technique C). However, for patients being treated with single-session PCDT (Techniques A and B, which involve more clot manipulation), there is sparse data to support or refute the use of IVC filters and limited evidence suggests that major PE can occur as a PCDT complication (67,68,87). Therefore, in ATTRACT, a retrievable Tulip filter (Cook Inc., Bloomington, IN) may be used at physician discretion if there is IVC and/or iliac vein thrombus and single-session PCDT is being used.

2. Balloon Maceration, Aspiration Thrombectomy, Rheolytic Thrombectomy, and Infusion CDT: As in routine clinical practice, after initial PCDT the physician may inflate a standard angioplasty balloon within any residual thrombus to macerate it and increase its surface area in order to enable rt-PA delivery to otherwise-inaccessible parts of the thrombus (63). A standard 7-8 French catheter and/or the AngioJet Rheolytic Thrombectomy System may be used to aspirate residual venous thrombus in order to improve flow and thereby prevent the complication of early re-thrombosis. Additional rt-PA bolus doses (up to 5mg per session) may be given. If there is still significant obstructing thrombus after the use of these measures, the physician may initiate (or for Technique C patients, continue) a continuous rt- PA infusion via a multisidehole infusion catheter at 0.01 mg/kg/hr (maximum allowable dose 1.0 mg/hr) for a maximum of 24 hours for Techniques A and B, or for a total maximum infusion time (including previous infusion) of 30 hours for Technique C. In all cases, the total rt-PA dose given for the entire treatment (all sessions together) may not exceed 35mg.
3. Balloon Angioplasty and Stent Placement: As in routine clinical practice, balloon angioplasty and stent placement may be performed to correct areas of venous stenosis or obstruction that persist after PCDT since these lesions, when not treated, have been associated with high rates of immediate re-thrombosis (49,63,92,93). These procedures are widely considered to represent standard care in patients undergoing PCDT (30,63). Although the decision to perform these procedures is left up to the physician, correction of lesions which are associated with ≥ 50% venous diameter narrowing, robust filling of collaterals on venography, and/or a measured mean pressure gradient exceeding 2 mmHg is encouraged. Per accepted practice, stents may be used in the iliac vein, and/or common femoral vein. Stent placement in the femoral or popliteal vein is strongly discouraged. If stents are placed, the use of self-expandable bare stents with radial flexibility, sized to the vein's expected diameter (usually 10-16 mm) or 1 mm larger, is recommended (63).

6.2.6 Allowed Concomitant Drug Therapies

During PCDT, subjects will receive anticoagulant therapy with either UFH or LMWH, as selected by the endovascular physician (see Section 7.3.1). For subjects receiving UFH who require continuous rt-PA infusions (either for clean-up of residual thrombus after initial use of Techniques A or B, or during Technique C), the UFH dose will be reduced to subtherapeutic levels as noted in Section 6.2.3.3. Subjects may continue medications for their other medical problems. If a subject is already on warfarin and is randomized to PCDT, the warfarin will be discontinued and Vitamin K may be given to bring the INR to 1.6 or below before PCDT.

6.2.7 Prohibited Concomitant Drug Therapies

The use of platelet glycoprotein IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide), fondaparinux, rivaroxaban, dabigatran, or other oral thrombin inhibitors during or within 24 hours before or after PCDT is not permitted. The use of aspirin, oral thienopyridine anti- platelet drugs, and non-steroidal anti-inflammatory drugs is discouraged while subjects are receiving anticoagulant therapy unless there is a compelling indication.

6.2.8 Crossover, Re-Treatment with PCDT, and Use of Other Endovascular Interventions

Experimental Arm subjects who develop symptomatic acute re-thrombosis in the iliac, common femoral, and/or femoral vein of the treated limb within the first 3 months after randomization may be re-treated with PCDT using the methods described in this protocol, if re-treatment would be consistent with the physician's standard practice and the patient's wishes. To be eligible for such re-treatment with PCDT, the patient's clinical presentation should be consistent with an acute re-thrombosis occurring within the last 14 days. Prior to re-treatment, the patient's clinical status should be re-evaluated. Re-treatment with PCDT should not be performed if the patient meets any one (or more) of the following Exclusion Criteria (Section 4.3): #6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, or 20. No more than two re-treatments should be performed in any patient. Any planned deviation from these guidelines should first be discussed with the Principal Investigator.

In all other situations (i.e. Experimental Arm subjects beyond 3 months after randomization, and Control Arm subjects anytime), the use of PCDT is strongly discouraged in the absence of limb-threatening circulatory compromise. If a Control Arm subject is judged to require PCDT, the Principal Investigator should be notified before PCDT is performed to ensure that this decision is adequately justified and documented. During follow-up, the use of other endovascular treatments (e.g. iliac vein stent placement as a stand- alone treatment) is strongly discouraged in all subjects absent a compelling indication.

Subjects in either treatment Arm who require endovascular intervention for treatment of severe symptomatic venous disease in the index leg during follow-up (except Experimental Arm patients being re- treated with PCDT within the first 3 months after randomization) will be asked to undergo a standardized clinical assessment for PTS (Section 8.9) before being treated. If the intervention is performed more than 6 months post-randomization, then the findings of this assessment will be used in evaluating whether the subject has PTS for the final analysis, per the guidelines in Sections 15.2 and 15.3.7. If this clinical assessment cannot be done, subjects who undergo an endovascular venous intervention in the index leg more than 6 months post-

randomization will be adjudicated as having severe PTS at the time that the endovascular procedure was performed, per Sections 15.2 and 15.3.7. Subjects who have an endovascular procedure during follow-up will continue to be followed and assessed as per the study protocol.

7 TREATMENT PROCEDURES

In this section, a detailed, step-by-step description of how the study treatments should be administered to ATTRACT Trial subjects in the Experimental and Control Arms is provided.

7.1 Pre-Randomization Anticoagulant Therapy (Subjects in Both Arms)

As current recommendations are to anticoagulate patients with suspected DVT even before diagnostic testing, we expect most enrolled subjects to be anticoagulated before randomization (30). Otherwise-eligible DVT patients who are already anticoagulated are still eligible for the study if their symptom onset was within 14 days. After enrollment, the patient should be anticoagulated with one of the regimens listed in Section 6.1.1. To avoid unnecessary transitions, if the patient was already receiving one of these regimens, the physician is encouraged to simply continue it. In patients receiving UFH, the physician should ensure that dose adjustments are being made per the guidelines in Section 6.1.1.

7.2 Initial Management of Control Arm Subjects

Immediately after randomization, the patient should receive (or continue to receive) initial anticoagulant therapy via one of the regimens listed in Section 6.1.1. Warfarin should be initiated on the day of randomization (or continued if already started). Control Arm subjects should be encouraged to ambulate as tolerated and may be treated as outpatients at the physician's discretion (4). For inpatients, the timing of hospital discharge is at the discretion of the physician. Subjects should have blood drawn at least every third day for INR testing while they are receiving UFH or LMWH and should continue to receive these agents until the INR ≥ 2.0 on two consecutive draws at least one day apart (if the INR > 3.0, the UFH or LMWH may be stopped before the INR is shown to be ≥ 2.0 on a subsequent blood draw). The heparin should then be discontinued and the subject should continue to receive warfarin titrated to an INR of 2.0 - 3.0. The frequency of INR monitoring should be reduced as a stable warfarin dose is established, per the medical co-investigator, with a maximum of 4 weeks between successive INR tests (30). The duration of anticoagulant therapy and the use of alternative regimens during follow-up are described in Section 6.1.2.

7.3 Initial Management of Experimental Arm Subjects

7.3.1 Anticoagulant Therapy in Experimental Arm Subjects

The physician may use UFH or twice-daily LMWH, per Section 6.1.1, as concomitant therapy during PCDT. To minimize the potential for bleeding, the guidelines below should be followed:

1. If **UFH** is being used as the primary anticoagulant drug during PCDT:

   Before starting PCDT: The UFH dose should be adjusted to therapeutic levels by institutional nomogram. At least one PTT (or anti-Xa activity level on a heparin assay, as noted in Section 6.1.1) must be available pre-procedure to ensure that the UFH level will not be supra-therapeutic at the time of PCDT. If the physician's plan is to use UFH as the primary anticoagulant drug during PCDT and the subject was recently receiving LMWH, the physician should wait until at least 8 hours after the last twice-daily LMWH dose, or 18 hours after the last once-daily LMWH dose, before starting PCDT.

   During the on-table portion of the PCDT procedure: The UFH dose should be targeted to a therapeutic PTT level (corresponding to 0.3 – 0.7 IU/ml anti-Xa activity on the site's heparin assay). Subjects may receive supplemental bolus doses of UFH (up to 50 units/kg) during PCDT at physician discretion. However, particular caution should be exercised in giving additional UFH doses to patients who are already therapeutically anticoagulated.

   During continuous rt-PA infusion: The UFH dose should be reduced to 6-12 units/kg/hr (maximum allowable dose 1000 units/hr) and the PTT maintained at less than 2 times control (there is no lower limit for PTT), or less than 0.5 IU/ml anti-Xa, for that institution. Infusion of UFH directly into the target limb via the sheath is encouraged to ensure the highest heparin concentration in the leg veins. Blood should be drawn at least every 6-8 hours for measurement of PTT or anti-Xa activity level.

2. If **LMWH** is being used as the primary anticoagulant drug during PCDT:

   Before starting PCDT: One of the twice-daily regimens described in Section 6.1.1 should be used. If the patient is already receiving LMWH, the physician should just continue the injections according to the currently planned schedule. If the physician plans to use LMWH as the primary anticoagulant drug during PCDT and the subject was recently receiving UFH, the physician should wait until at least 3 hours after UFH cessation or until the level is shown to be subtherapeutic by a PTT level $\leq$ 1.5 times control (or a anti-Xa activity level $\leq$ 0.3 IU/ml), before starting PCDT. If the patient was

not already receiving LMWH but was receiving UFH, the first LMWH dose may be administered at physician discretion as long as the UFH level is not supratherapeutic as determined by PTT or anti-Xa activity level assay.

During the on-table portion of the PCDT procedure: Subjects may receive supplemental bolus doses of UFH (up to 50 units/kg) during PCDT at physician discretion. However, caution should be exercised as these patients are already therapeutically anticoagulated.

During continuous rt-PA infusion: The twice-daily LMWH doses should be given on schedule. Additional UFH should not be given, except for very low doses that may be present within sheath flush solutions, not to exceed 200 units/hour total to the patient.

7.3.2 Subject Preparation for PCDT Procedures

1. Steroid Pre-Medication: In subjects with contrast allergies, steroid pre-medication should be started 12-24 hours before PCDT, per the Center's standard practice. A histamine receptor antagonist (e.g., diphenhydramine) should also be given before contrast is administered. Both the steroids and the histamine receptor antagonist should be continued throughout the period when contrast may be administered (i.e., for multi-session procedures).
2. Reversal of Elevated INR: In subjects with an INR > 1.6, Vitamin K should be given orally, subcutaneously, or by intravenous infusion to bring the INR to 1.6 or below before PCDT.
3. Pre-procedure Hydration: Subjects should receive pre-procedure hydration as dictated by their renal function, overall clinical status, and the physician's standard practice.
4. IVC Filter Placement: As outlined in Section 6.2.5, in selected subjects a retrievable IVC filter may be placed at the endovascular physician's discretion. The filter may be placed per the institution's standard practice at any time before PCDT, with these caveats:
   a) An ultrasound-guided venous access should be used. If the filter is placed within 48 hours before PCDT, a venous sheath or catheter should be left in place until at least 1 hour after the last administration of rt-PA (to avoid puncture site bleeding).
   b) An IVC venogram must be obtained to ensure accurate filter deployment.
   c) Non-ionic iodinated contrast should be used to minimize risk to the kidneys.
   d) A retrievable Tulip filter (Cook Inc., Bloomington, IN) should be used.
   e) The filter should be deployed in the infrarenal IVC, if possible.

7.3.3 Phase 1 - Procedure Initiation

PCDT procedures should be initiated using the following accepted endovascular practices (63):

1. The endovascular physician should review the baseline imaging studies, examine the affected lower extremity with ultrasound, and select a primary venous access site.
2. An intravenous line should be placed and conscious sedation initiated with continuous monitoring of heart rate, oxygen saturation, blood pressure, and cardiac rhythm.
3. Sterile technique must be used during all endovascular procedures.
4. Local anesthesia should be injected into the skin over the venous access site(s).
5. Catheter access into the deep venous system should then be obtained – this must be done using ultrasound-guided puncture (to prevent inadvertent arterial punctures) of the selected lower extremity vein (e.g., the ipsilateral popliteal vein) or the right internal jugular vein. The physician may access additional veins under ultrasound guidance at his/her discretion. The physician is strongly encouraged to choose a venous access strategy that will enable direct treatment of any popliteal and/or below-knee thrombus that is needed to ensure adequate inflow into the proximal veins. The use of the contralateral common femoral vein for access is, however, strongly discouraged. The use of the femoral vein in the mid-thigh is prohibited.
6. Real-time fluoroscopic monitoring of catheter/guidewire manipulations should be used.
7. A catheter should be advanced into the venous system and a baseline venogram of the proximal veins (popliteal vein through infrarenal IVC) should be obtained with digital imaging and serial hand-injections of 5-10 ml non-ionic iodinated contrast, diluted as needed with normal saline, through the catheter at 10-20 cm intervals. Automated power injection is not permitted. **Note:** As the thrombus extent on the baseline venogram is relevant to the study data analysis, care should be taken to obtain complete imaging of the thrombus extent, even if this requires contrast injections from within non-flowing iliac or femoral venous segments.
8. The endovascular physician should examine the venogram. Based upon the presence or absence of good popliteal vein inflow and IVC thrombus, the physician should follow the guidelines provided in Section 6.2.4 to determine which PCDT technique must be used.
9. The catheter should be exchanged for a vascular sheath to maintain deep venous access and to enable repeat venograms to be performed to monitor thrombolytic progress.

7.3.4 Phase 2 - Performance of Initial PCDT

1. Initial PCDT: The steps in **Appendix 4** (for Trellis PCDT)**, Appendix 5** (for AngioJet PCDT)**,** or **Appendix 6** (for Infusion-First PCDT) should then be followed to deliver rt-PA into the thrombus. After completion of those steps, proceed to the steps in Section 7.3.5 below.

2. Treatment Cessation or Reduction of rt-PA Dose: During PCDT, the physician may reduce the rt-PA dose or stop it entirely at his/her discretion if there are safety concerns. If serious bleeding occurs at the venous access site (uncontrolled by sheath upsizing or compression), rt-PA administration should be stopped. If sheath upsizing and/or compression are effective in stopping the bleeding, rt-PA may be re-started at a lower dose. If serious bleeding occurs in a distant location, or if a severe or life-threatening reaction occurs, administration of rt-PA should be permanently stopped. If serious bleeding occurs, infusion of UFH should also be stopped and, at physician discretion, protamine and/or cryoprecipitate may be given.

7.3.5 Phase 3 - Clean-Up of Residual Thrombus

1. A repeat venogram should be obtained through the sheath or a catheter. If near-complete (> 90%) lysis and good anterograde flow are observed (by visual estimation) with no venous stenosis or obstruction, treatment may be stopped at any time thereafter at the physician's discretion – in this situation, proceed to Section 7.3.7. If near-complete (> 90%) lysis is observed but there is significant venous stenosis or obstruction, proceed to Section 7.3.6.

2. If residual thrombus is present, the physician may use the following adjunctive measures. To minimize the risk of causing PE, these methods should not be used prior to completion of initial PCDT (Techniques A and B) or at least 4 hours of rt-PA infusion (Technique C). The decision as to which method(s) are used, and the sequence, may be determined by the physician to allow maximum flexibility to tailor therapy to individual patient circumstances.

    a) Balloon Maceration of the thrombus may be performed as follows: Advance a standard angioplasty balloon catheter (6-10 mm for the femoral vein, 10-12 mm for the common femoral vein or iliac vein) over the guidewire into the thrombus. Inflate the balloon within the thrombus under fluoroscopic guidance using the physician's usual technique. Deflate the balloon. Repeat these steps as needed with the balloon positioned in different parts of the thrombus. Remove the

angioplasty balloon catheter over the guidewire.

b) Aspiration thrombectomy may be performed as follows: Advance a standard 7-8 French catheter over the guidewire to the cephalad aspect of the thrombus. Attach a large (30- 60 ml) syringe to the catheter. Vigorously aspirate with the syringe during withdrawal of the catheter through the thrombus – this may be done with the guidewire in place or with the guidewire removed. Repeat these steps as needed, then remove the catheter.

c) Rheolytic thrombectomy may be performed using the AngioJet in aspiration mode, as described in **Appendix 5**, Steps 5-9. The precautions cited in **Appendix 5** regarding guidewire retraction, infusate volume, and device activation time should be followed.

d) Additional rt-PA boluses (up to 5 mg rt-PA per session) may be given at the physician's discretion, but **the total rt-PA dose may not exceed 35mg for all sessions combined**. The additional rt-PA may be delivered in the following ways: (1) via injection through the vascular sheath or a multisidehole catheter; (2) in Technique A patients only, via the Trellis as described in **Appendix 4**, Steps 4-8; or (3) in Technique B patients only, via the Angiojet (PowerPulse or Rapid Lysis method) as described in **Appendix 5**, Step 4.

3. Perform a repeat venogram. If significant residual obstructing thrombus is present, position a multisidehole infusion catheter within the thrombus and perform Infusion CDT (rt-PA at 0.01 mg/kg/hr, maximum dose 1.0 mg/hr) as outlined in **Appendix 6**. (For Technique C subjects, this will simply represent a continuation of the initial rt-PA infusion.) The rt-PA infusion should continue until near-complete (> 90%) thrombolysis is observed, clinically-overt bleeding becomes evident, or until a maximum of 24 hours (for Technique A or Technique B) or 30 hours total (for Technique C) of rt-PA infusion has occurred.

4. The steps in Section 7.3.5 may be repeated as needed, but the above limits on rt-PA dose, infusion duration, device activation time, and AngioJet infusate volume must be followed.

7.3.6 Phase 4 - Treatment of Obstructive Lesions

1. At physician discretion, balloon angioplasty and/or stent placement may be performed to correct areas of venous stenosis or obstruction, pursuant to the guidelines in

Section 6.2.5.

2. Venography should be repeated after balloon angioplasty and/or stent placement.

7.3.7 Phase 5 - Completion of PCDT Procedures

1. The physician should perform a venogram that documents the status of the proximal deep veins (popliteal vein through IVC). **Note:** As the thrombus extent on the final venogram will be analyzed as a study outcome, care should be taken to obtain complete imaging of the extent of thrombus, even if this requires contrast injection from within non-flowing segments.
2. When therapy is completed, the sheath may be removed at the physician's discretion, but no less than 1 hour after the last rt-PA dose or UFH bolus dose was given. Hemostasis should be achieved via manual compression. The subject should remain at bedrest with the treated leg immobile for 6 hours, after which he/she may ambulate as tolerated.
3. Therapeutic-level anticoagulation should be resumed within 2 hours after hemostasis is obtained. If UFH is used, a bolus dose should not be given. Subjects receiving LMWH should continue their previous regimen of scheduled injections.
4. Warfarin should be initiated on the same day as sheath removal. Warfarin intensity, duration of therapy, INR monitoring, overlap with heparin therapy, and hospital discharge should be managed in the same way as in the Control Arm (Section 7.2). However, PCDT subjects may not be discharged from the hospital until at least 12 hours after sheath removal.
5. For subjects in whom a retrievable IVC filter was placed prior to PCDT, careful attention should be paid to ensuring timely removal of the filter. The filter may be removed at any time interval after PCDT that is consistent with safe clinical practice. In general, removal of the filter as soon as possible (e.g. within 3 days) after completion of PCDT is encouraged. If this cannot occur, the subject should be assessed at the 10-day follow-up visit for the ability to have the filter removed, and similarly re-assessed at least every 3 weeks thereafter until the filter has been removed or 3 months have elapsed since the date of its original insertion. There is no need to stop anticoagulation for filter retrieval unless it is supra-therapeutic. The retrieval may be performed per the physician's standard practice, but an ultrasound-guided jugular vein approach should be used to avoid inadvertent arterial punctures and trauma to the leg veins. Two conditions should be met before filter retrieval: (a) the subject must be therapeutically anticoagulated; and

(b) on venography or contrast-enhanced CT scan, the subject must not have significant thrombus within the filter (≥ 25% of the filter's volume) or within the IVC below the filter (94,95). If either condition is not met, the filter should be left in place and removed when these criteria are satisfied. The filter should only be left in place permanently in the following situations: (a) the patient has a strong indication for long-term caval interruption, per the criteria outlined in Section 6.1.4; (b) the filter proves to be difficult to remove without extensive catheter manipulation that would risk injury to the caval wall; or (c) the filter could not be removed within 3 months after the date of its original insertion.

8 EFFICACY OUTCOMES

8.1 Primary Efficacy Outcome

Post-Thrombotic Syndrome (PTS) defined by the presence of a total score of 5 or greater on the Villalta PTS Scale in the leg with the index DVT, or an ulcer in that leg, that occurs at any time between the 6-month post-randomization follow-up visit and the 24-month visit (inclusive).

8.2 Secondary Efficacy Outcomes

- PTS occurrence at 6, 12 and 18 months, assessed using Villalta PTS Scale (as above).
- Major non-PTS treatment failure during 24 months (see Section 15.3.7 for definition)
- Composite of PTS occurrence + major non-PTS treatment failure during 24 months
- PTS severity at 6, 12, 18 and 24 months, assessed using:
  a) Villalta PTS Scale
  b) Venous Clinical Severity Score (VCSS)
  c) Clinical Class in the Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) System.
- Quality of Life (QOL) at 1, 6, 12, 18 and 24 months, assessed using:
  a) SF-36v2 measure (general QOL)
  b) VEINES-QOL/Sym measure (venous disease-specific QOL).
- Resolution of leg pain at 10 days and 1 month, assessed using Likert scale scores.
- Resolution of leg swelling at 10 days and 1 month, assessed using standardized measurement of calf circumferences.
- Degree of clot lysis with PCDT, assessed venographically (Experimental Arm only).
- Prevalence of valvular reflux and residual thrombus at 1 year (Duplex ultrasound).
- Cost-effectiveness, measured in dollars per quality-adjusted life-year (QALY).

8.3 Diagnosis of PTS

PTS is a “syndrome” that produces a range of symptoms and clinical signs which differ in character and severity among patients (6). There is no “gold standard” criterion test to establish the diagnosis of PTS. In fact, correlations between “objective” findings on non-invasive tests and clinically important PTS disease have been poor-to-moderate (96,97). For example, valvular reflux is usually present on Duplex ultrasound in patients with PTS, but many patients with reflux do not have PTS symptoms, health impairment, or poorer QOL (26,96). As such, the diagnosis of PTS should not be based upon imaging or physiological findings alone. In clinical practice, PTS is diagnosed using clinical criteria (assessment of symptoms and clinical signs).

8.4 Justification of 24-Month Period for PTS Assessment

We adopted a 24-month follow-up period for assessment of PTS to ensure that we will not miss incident PTS cases due to insufficient duration of follow-up. As prospective studies have shown that 83-96% of PTS cases manifest by 2 years (2,3,5,31), we expect to miss very few cases. Two years also allows enough time for the more severe PTS manifestations to develop.

8.5 Selection of PTS Measures

A number of clinical scales have been developed to standardize the diagnosis of PTS and to rate its severity. Because there is no gold standard test for PTS, validation of PTS measures has relied upon showing that they correlate with important health outcomes such as quality of life, and with known anatomic/physiologic findings of chronic venous disease. In selecting the Villalta PTS Scale as our primary outcome measure, we placed high value upon its proven ability to identify subjects with clinically significant PTS after first-episode, proximal DVT. A detailed description of the evidence supporting Villalta PTS Scale is provided in **Appendix 7**. To enhance interpretation of the trial results, we will also use two additional measures which were designed to standardize the descriptive classification of chronic venous disease (CEAP Classification System) and to grade its severity (Venous Clinical Severity Score).

8.6 The Villalta PTS Scale

The Villalta PTS Scale (**Appendix 8**) rates the severity of 5 patient-reported symptoms (pain, cramps, heaviness, paresthesia, pruritus) and 6 clinician-observed signs (edema, skin induration, hyperpigmentation, pain during compression, venous ectasia, redness) of PTS on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). The points are summed into a total score (range 0-33) for each leg (98). Subjects are categorized as having PTS if the total score in the leg with the index DVT is 5 or greater, or if an ulcer is present in that leg, at any time between the 6-month and the 24-month follow-up visits (see Section 6.2.8 and Section 15.2 for

circumstances in which PTS may be diagnosed before the 6-month follow-up visit in subjects who undergo unscheduled endovascular procedures). Subjects will also be categorized as having mild (score 5-9), moderate (score 10-14), or severe PTS (score >15 or leg ulcer).

8.7 Clinical-Etiologic-Anatomic-Pathologic (CEAP) Classification System

All subjects will have their Basic CEAP Clinical Class assessed for each limb (99,100). The limb will be categorized into one of 8 descriptive "Clinical Classes" based upon the dominant physical exam findings observed (101) (see **Appendix 9**):

C0 = no disease
C1 = telangiectasias or reticular veins
C2 = varicose veins
C3 = edema
C4a = pigmentation or eczema
C4b = lipodermatosclerosis or atrophie blanche
C5 = healed venous ulcer
C6 = active venous ulcer

Subjects will be assigned the highest Class for which they have a component sign, and will be classified as symptomatic (S) or asymptomatic (A). The ascending severity of the Clinical Classes has been shown to correlate with QOL (102,103). In ATTRACT, the Etiologic ("E"), Anatomic ("A") and Pathophysiologic ("P") components of the CEAP System will not be used.

8.8 Venous Clinical Severity Score (VCSS)

The VCSS is a 30-point venous severity scoring system (104-107). Its components were derived from selected elements of CEAP (eight clinical signs and one symptom of chronic venous disease) that exhibit change over time. Extra weight was given to signs from the more severe (C4–C6) CEAP classes (**Appendix 10**). Use of the VCSS should improve our ability to distinguish subjects with different severities of PTS and to assess PCDT's cost-effectiveness.

8.9 Administration of PTS Measures

The Villalta PTS Scale will be administered to subjects at baseline and at the 10-day and the 1, 6, 12, 18, and 24-month follow-up visits. CEAP and VCSS will be administered to subjects at the 6, 12, 18 and 24-month follow-up visits. Prior to initial use, examining clinicians will complete training and certification on their proper administration to ensure uniform administration across all Clinical Centers. The examiners must be blinded to the subjects' treatment allocation.

The day before follow-up visits, subjects should receive a telephone reminder to not wear compression stockings on the day of the visit, and to <u>not</u> reveal to clinic staff which therapy they received (PCDT or no PCDT) and which leg was affected with the DVT. Subjects should be examined in the afternoon (the later the better) to allow the symptoms and signs of PTS to

manifest. At the time of assessment, the following procedures should be followed:

1. The subject should be asked to rate (absent, mild, moderate, severe) the 5 symptoms on the Villalta PTS scale for each leg, record his/her ratings on the Villalta PTS Symptoms Form, and also complete the QOL Questionnaire (see below) and Leg Pain Severity Form.
2. The subject should be brought to a well-lit examining room. The subject's legs should be unclothed and he/she should be seated facing the blinded clinician (nurse or physician).
3. Subsequently, and without access to the subject's rating of symptoms, the blinded clinician should assess the clinical signs required for Villalta, CEAP, and VCSS measures; measure the leg circumference; and record these results on the respective Case Report Forms.
4. The blinded clinician should check that all scales have been filled out correctly and completely before the subject leaves. If there are missing items, the blinded clinician should ask the subject (without coercion) if he/she would like to complete the form.

Measurement scales will be available in English and Spanish. If subjects have difficulty completing forms (e.g., language barrier, visual impairment, literacy), blinded study personnel or a translator should assist, taking care to avoid influencing the subject's responses.

8.10 Health-Related Quality of Life (QOL)

We will assess general and venous disease-specific QOL at baseline and at the 1-month, 6-month, 12-month, 18-month and 24-month follow-up visits.

8.10.1 General QOL

General QOL will be measured using the Short-Form Health Survey-36, Version 2 (SF-36v2), a validated, widely-used gold standard instrument (108). The SF-36 has been used in other DVT studies to complement measures of PTS and venous disease-specific QOL (10,12,102,109). The SF-36v2 will be available for use in both English and Spanish versions.

8.10.2 Venous Disease-Specific QOL

Venous disease-specific QOL will be measured using the VEINES-QOL/Sym measure, a patient self-assessment questionnaire (110). The instrument consists of 25 question items that measure venous symptoms, limitations in daily activities due to venous disease, psychological impact of venous disease, and change over the past year. Responses are rated on 2-point to 7- point Likert scales of intensity, frequency, or agreement. The VEINES-QOL/Sym has undergone comprehensive and rigorous psychometric evaluation and is acceptable, reliable, valid, and responsive for use as a patient-reported measure of outcome in studies of chronic venous

disease, including PTS and DVT (109-111). The VEINES-QOL/Sym measure will be available in the originally validated English version and in a certified Spanish translation.

8.10.3 Administration of QOL Instruments

The SF-36 and VEINES-QOL/Sym will be combined into a single questionnaire that takes 15-20 minutes for an average patient to complete (**Appendix 11**). Following a standard orientation, the subject will complete the questionnaire in a quiet office. The study nurse will then check for missing data and politely (without coercion) encourage the subject to respond to all items. The nurse administering the questionnaire must be blinded to the subject's treatment allocation.

8.10.4 Scoring of QOL Instruments

QOL data will be scored by blinded DCC personnel using established computer algorithms which include imputation of missing data (112,113). Summary scores will be computed for the SF-36 Physical (PCS) and Mental (MCS) Component Scales, and for the VEINES-QOL (impact of venous disease upon QOL) and VEINES-Sym (symptom severity) summary scales.

8.11 Resolution of Leg Pain and Swelling

To determine if PCDT leads to faster DVT symptom resolution, the severity of pain in each leg will be assessed on a 7-point Likert scale at baseline and 10-day and 1-month follow-up. The subject will be asked to "Please rate the overall intensity of "pain" or "discomfort" that you have felt in your leg during the past 24 hours by checking one response on the following scale" (1 = No pain, 2 = Very mild pain, 3 = Mild pain, 4 = Moderate pain, 5 = Severe pain, 6 = Very severe pain, 7 = Extremely severe pain). Likert scales are widely validated for pain severity assessment (114,115). The Likert scale and accompanying instructions will be available in the originally validated English version and in a certified Spanish translation. Calf circumference 10cm below the tibial tuberosity will also be measured at baseline and 10-day and 1-month follow-up. At these visits, venous symptoms and signs will also be assessed using the Villalta PTS Scale. The clinician performing these assessments must be blinded to subject treatment allocation.

8.12 Venographic Thrombus Extent (Experimental Arm Only)

Two sets of venograms will be analyzed in each Experimental Arm subject: (a) the baseline venogram of the proximal veins (popliteal vein through infrarenal IVC) obtained after initial catheter insertion into the venous system and before PCDT; and (b) the final venogram of the proximal veins obtained after PCDT and any adjunctive procedures, and before sheath removal. The primary goal of the venogram evaluation is to determine the degree of thrombus elimination and correlate it with the likelihood of developing PTS. The venograms will be transmitted to the DCC and initially evaluated for overall quality in standardized fashion by blinded Independent

Adjudication Committee physicians who are experienced with venogram adjudication in DVT trials. Feedback to Clinical Centers will be provided when inadequate exams are identified in order to encourage better quality venography in subsequent subjects. Readers will quantify clot burden using the components of the Marder score that describe the proximal veins (116).

8.13 Ultrasound Substudy - Valvular Reflux and Residual Thrombus

A 1-year follow-up venous Duplex ultrasound of the index leg will be performed in a consecutive 142-subject subgroup in 7 Clinical Centers. The primary goal of the Ultrasound Substudy will be to determine if prevention of valvular reflux and/or venous obstruction from residual thrombus represents a primary mechanism underlying any effect of PCDT upon the cumulative incidence and severity of PTS. We will assess: (a) the presence of valvular reflux (flow reversal for ≥ 0.5 seconds after standardized distal compression with an automatic cuff inflator) in the common femoral, deep femoral, femoral, popliteal, great saphenous, and small saphenous veins (117,118); and (b) the presence of residual thrombus (assessed in the leg veins mainly by incomplete compressibility) in the iliac, common femoral, deep femoral, femoral, popliteal, and great saphenous veins (77). Reflux will be evaluated with subjects standing and bearing weight on the contralateral limb (see **Appendix 12** for recommended ultrasound exam protocol). The exams must be performed in standardized fashion by Clinical Center sonographers blinded to treatment allocation, recorded in real time on super VHS videotapes or digital media, and transmitted to the Ultrasound Core Laboratory. Blinded Core Lab personnel will analyze the exams for overall quality, interpret findings, record them on an Ultrasound Case Report Form (CRF), and transmit it to the DCC. At the DCC, reflux and obstruction will be quantified from the CRFs by blinded personnel using the Venous Segmental Disease Score (VSDS) in which values assigned to the presence of reflux and obstruction in specific lower extremity veins are summed to yield a Reflux Score and an Obstruction Score (102,106,107).

9 SAFETY OUTCOMES

The following safety outcomes will be assessed for each subject over the 24-month period.

- Major bleeding and minor bleeding
- Need for transfusion
- Intracranial bleeding
- Symptomatic pulmonary embolism
- Symptomatic recurrent venous thromboembolism
- Mortality

9.1 Bleeding

Evaluation of clinically overt bleeding will depend upon the suspected bleeding site. For example, subjects with suspected intracranial bleeding will undergo a head CT scan and subjects with suspected retroperitoneal bleeding will undergo a CT scan of the abdomen/pelvis. Clinically overt bleeding will be classified as “Major” if it is associated with a fall in the hemoglobin level of at least 2.0 g/dl, transfusion of ≥ 2 units of red blood cells, or involvement of a critical site (e.g. intracranial, intraspinal) (119). Less severe clinically overt bleeding will be classified as minor. To distinguish clinically important hemorrhage from hemoglobinuria (which is routinely observed in subjects undergoing mechanical thrombectomy), discoloration of the urine during or after mechanical thrombectomy will not by itself be considered to indicate the presence of clinically-overt bleeding. Major bleeding, minor bleeding, need for transfusion, and intracranial bleeding will be assessed during the study period and reported. To aid in evaluating the relationship of bleeding events to rt-PA administration, they will also be categorized by whether they occurred within 3 days after the initiation of PCDT. Data on complications will be captured on the Case Report Forms in a way that enables their outcomes to be categorized according to FDA guidelines and SIR reporting standards (48,120).

9.2 Symptomatic Pulmonary Embolism (PE)

When PE is clinically suspected, spiral CT of the pulmonary arteries and/or ventilation-perfusion lung scan will be obtained. If there is a new intraluminal filling defect of a segmental or more central pulmonary artery or a "high probability" perfusion defect, PE will be diagnosed. PE will be excluded if the spiral CT is normal or there are no perfusion defects. If the perfusion scan or CT scan is non-diagnostic, bilateral lower extremity ultrasound will be performed and PE will be diagnosed if there is new DVT (see next section). Ultrasound will be repeated after 7 $\pm$ 2 days if there is no new DVT. Pulmonary angiography may be performed if there are equivocal findings and/or serial ultrasound testing is considered unsafe. To distinguish clinically important new PE events from minor symptoms of PE events that may have occurred prior to randomization, and from the clinical findings of micro-embolization that are commonly observed during thrombolytic therapy (e.g. transient pleuritic chest pain that resolves completely), investigation for PE during the first 10 days after enrollment is discouraged (in subjects in both study arms) in the absence of more significant clinical findings that suggest a new symptomatic PE event. Symptomatic PE events will be assessed during the 24-month study period and reported.

9.3 Symptomatic Recurrent DVT

To increase the accuracy of diagnosing recurrent DVT, there will be standardized recording of

the extent of thrombus (diameters of the common femoral vein and popliteal vein and the thrombus' proximal and distal extent) on the baseline (strongly recommended when the exam is performed locally) and 1-month follow-up (this information is required) ultrasound exams. When recurrent DVT is clinically suspected during follow-up, compression ultrasound of the proximal veins (popliteal vein to common femoral vein) will be performed and a Compression Ultrasound CRF documenting the exam will be transmitted by the Clinical Center to the DCC. If there was no DVT on the last ultrasound (or on the last venogram performed during follow-up) of the same leg, recurrent DVT will be diagnosed using the same criteria as that of a qualifying proximal DVT (Section 4.4). If a previous ultrasound or a follow-up venogram is available for comparison, recurrent DVT will be diagnosed if one of the following criteria is met: (a) there is a new non-compressible common femoral, femoral, or popliteal vein; (b) there is ≥ 10cm extension of thrombus margin (i.e. transition from not fully compressible to normal); or (c) there is a 4-mm increase in compressed thrombus diameter at the common femoral vein or popliteal vein (77,119,121-124). If these criteria are not met, DVT will not be diagnosed and, if there is still uncertainty about the presence of recurrent DVT (e.g. moderate or high clinical suspicion for recurrent DVT; non-diagnostic findings on ultrasound), the ultrasound should be repeated after 7 $\pm$ 2 days, and judged by the same criteria. If the second test is not diagnostic for recurrence, DVT will be excluded. Venography or CT scan can be performed if, in the absence of diagnostic findings, clinical suspicion for recurrence is high or the ultrasound findings are equivocal. If the Clinical Center interpreted the study as either negative (no evidence of new DVT), or positive for DVT in a limb with no previous DVT, the Adjudication Committee will review the clinical information and Compression Ultrasound CRF and provide a final adjudication of the event. If the Clinical Center interpreted the study as positive for new DVT in a limb with previous documented DVT, or if there is difficulty with interpretation, the recent and last previous ultrasound studies will be reviewed by the Ultrasound Core Laboratory. Taking into account the Ultrasound Core Laboratory's review along with the clinical information and Compression Ultrasound CRF, the Adjudication Committee will then provide a final adjudication of the event. Symptomatic recurrent DVT will be assessed during the 24-month study period and reported. In the PCDT Arm, early (within 1 month) re-thrombosis of PCDT-treated vein segments will be distinguished from other recurrent DVT events.

9.4 Death

Cause of death will be determined from hospital and outpatient records, autopsy data, and other information. Death will be attributed to PE if it is unexplained and sudden or there is substantive supporting evidence. Mortality will be assessed during the 24-month study period and reported.

9.5 Clinical Events Adjudication

Data on suspected clinical events will be reviewed by two blinded adjudicators who are expert DCC clinicians with extensive experience in adjudicating clinical events for DVT trials. They will interpret data per the study adjudication manual, without knowledge of treatment allocation. If there is disagreement, a second adjudication will occur with three adjudicators to obtain consensus. If consensus is not obtained, two votes will be sufficient to adjudicate the outcome. To further blind the adjudicators, unknown to them suspected events from ATTRACT will be interspersed with suspected events from other treatment studies being adjudicated at the DCC.

10 HEALTH ECONOMIC OUTCOMES

As ATTRACT offers a good opportunity to estimate PCDT's cost-effectiveness, we will compare economic outcomes between subjects in the two study arms. If PCDT is found to be efficacious and associated with increased costs, we will do a formal cost-effectiveness analysis to estimate the incremental cost per quality-adjusted life year (QALY) gained with PCDT (**Appendix 13**).

10.1 Medical Resource Utilization and Costs

Data relating to direct and indirect costs will be collected for each subject. For the index hospitalization, costs will be estimated using a combination of: (a) procedural resource use data for major cost drivers, from which costs will be calculated using standard resource-based costing methods; and (b) hospital billing data, which will be converted to costs based on department level cost to charge ratios. A similar approach will be used to assess costs associated with hospitalizations during follow-up. For other aspects of follow-up medical care, we will assess detailed resource utilization at each follow-up clinic visit and apply a variety of approaches including the Medicare fee schedule (for outpatient physician services, rehabilitation and skilled nursing services) and average wholesale prices (for medication costs). Indirect costs will be estimated from data relating to lost time from work, decreased productivity, and informal caregivers' time associated with loss of functional independence. Assessment of outpatient resource utilization and indirect costs will be aided by the use of a "cost diary", which each ATTRACT subject will use to record (weekly) outpatient medical encounters, travel time, and out of pocket expenses related to their DVT. Cost diaries will be available in English and Spanish.

10.2 Utility Measurement

Although QOL will be assessed using a variety of disease-specific and generic instruments in ATTRACT, for the purposes of economic analysis QOL will be assessed in terms of utility-- a

measure of an individual's preference for his or her current health state relative to perfect health on a 0-1 scale (125). Although in the past, it had been customary to measure utility directly from the trial participants using time-tradeoff techniques, there is an emerging consensus that cost-effectiveness analyses designed to inform societal resource allocation should use community-based (rather than patient-based) preferences (126). For ATTRACT, we will calculate preference-based utility scores from the SF-36v2 data being collected as part of the QOL study, using a recently-validated U.S.-specific scoring algorithm developed by Brazier et al (127). This method has the advantage of using population-based utility weights that are appropriate to the perspective of our analysis (i.e. U.S. societal weights).

10.3 Cost-Effectiveness Analysis

Although the trial will follow subjects for 24 months, outcomes pertinent to cost-effectiveness may continue to evolve well after its conclusion. In particular, we expect the benefits of PCDT to accrue over the long term through a reduction in PTS-related morbidity and costs. Hence, a method is required for converting the observed trial experience into corresponding lifetime quality-adjusted survival and costs for the incremental cost-effectiveness calculations. Although the use of "within-trial" cost-effectiveness ratios would eliminate the need for extrapolation, such an approach would bias our analysis substantially against PCDT given its high up-front cost and the expectation that any QOL benefits are likely to be sustained. To extend the trial results beyond the observed time-frame, we will develop a Markov (state-transition) model (128) in which the principal health states will describe the long-term complications of DVT as defined by the clinical trial (e.g., death, PE, recurrent DVT, venous ulcer). To the extent possible, data for this model will be based on the empiric results of ATTRACT and the published literature. In addition, the VETO Study, a 5-year Canadian study of 387 DVT patients that is collecting detailed clinical, resource use, and cost data related to PTS, will serve as a source of long-term cost transition probability and utility inputs for the model (81,129,130). Once the model is developed and validated using the ATTRACT data, we will use it to calculate an incremental cost-effectiveness ratio for the more expensive therapy (presumably PCDT) compared with the less expensive therapy, and by comparing this ratio with those of other medical interventions, determine which strategy is preferred on economic grounds.

11 FOLLOW-UP SCHEDULE

See **Appendix 14** for a schedule of study procedures and assessments.

11.1 Scheduled Visit 1 – Follow-Up Assessment at 10 Days

At 10 days ± 3 days after randomization, subjects:

- rate their leg pain (7-point Likert scale) (both legs)
- have their leg circumference measured (both legs)
- undergo assessment using the Villalta PTS Scale (both legs)
- are provided sized-to-fit elastic compression stockings (ECS)
- have their platelet count obtained to assess for heparin-induced thrombocytopenia (HIT)
- have adverse events, thrombotic and bleeding events, hospitalizations, physician visits, anticoagulant regimen, and their cost diary reviewed and recorded
- are re-assessed for removal of a retrievable IVC filter (if one is present)

11.2 Scheduled Visit 2 – Follow-Up Assessment at 1 Month

At 30 days ± 7 days after randomization, subjects:

- rate their leg pain (7-point Likert scale) (both legs)
- have their leg circumference measured (both legs)
- undergo assessment using the Villalta PTS Scale (both legs)
- complete a QOL questionnaire (SF-36v2, VEINES-QOL/Sym)
- have a bilateral lower extremity Duplex ultrasound exam
- are queried on their use of ECS, and then ECS use is reinforced
- have adverse events, thrombotic and bleeding events, hospitalizations, physician visits, anticoagulant regimen, and their cost diary reviewed and recorded
- are re-assessed for removal of a retrievable IVC filter (if one is present)

11.3 Scheduled Visit 3 – Follow-Up Assessment at 6 Months

At 6 months ± 1 month after randomization, subjects:

- undergo assessment using Villalta PTS Scale, CEAP and VCSS instruments (both legs)
- complete a QOL questionnaire (SF-36v2, VEINES-QOL/Sym)
- are queried on their use of ECS, and then ECS use is reinforced
- have adverse events, thrombotic and bleeding events, hospitalizations, physician visits, anticoagulant regimen, and their cost diary reviewed and recorded (Note: per Section 13.5, non-serious adverse events that started > 30 days after randomization (and > 30 days after a subsequent use of rt-PA, if applicable) should not be reported to the DCC)

11.4 Scheduled Visit 4 – Follow-Up Assessment at 12 Months

At 12 months ± 1 month after randomization, subjects:

- undergo assessment using Villalta PTS Scale, CEAP and VCSS instruments (both legs)
- complete a QOL questionnaire (SF-36v2, VEINES-QOL/Sym)

- are queried on their use of ECS, and then ECS use is reinforced
- have adverse events, thrombotic and bleeding events, hospitalizations, physician visits, anticoagulant regimen, and their cost diary reviewed and recorded (Note: per Section 13.5, non-serious adverse events that started > 30 days after randomization (and > 30 days after a subsequent use of rt-PA, if applicable) should not be reported to the DCC)
- have a lower extremity Duplex ultrasound of the index leg (if in the Ultrasound Substudy)

11.5 Scheduled Visit 5 – Follow-Up Assessment at 18 months

At 18 months ± 1 month after randomization, subjects:

- undergo assessment using Villalta PTS Scale, CEAP and VCSS instruments (both legs)
- complete a QOL questionnaire (SF-36v2, VEINES-QOL/Sym)
- are queried on their use of ECS, and then ECS use is reinforced
- have adverse events, thrombotic and bleeding events, hospitalizations, physician visits, anticoagulant regimen, and their cost diary reviewed and recorded (Note: per Section 13.5, non-serious adverse events that started > 30 days after randomization (and > 30 days after a subsequent use of rt-PA, if applicable) should not be reported to the DCC)

11.6 Scheduled Visit 6 – Follow-Up Assessment at 24 months

At 24 months ± 2 months after randomization, subjects:

- undergo assessment using Villalta PTS Scale, CEAP and VCSS instruments (both legs)
- complete a QOL questionnaire (SF-36v2, VEINES-QOL/Sym)
- are queried on their use of ECS, and then ECS use is reinforced
- have adverse events, thrombotic and bleeding events, hospitalizations, physician visits, anticoagulant regimen, and their cost diary reviewed and recorded (Note: per Section 13.5, non-serious adverse events that started > 30 days after randomization (and > 30 days after a subsequent use of rt-PA, if applicable) should not be reported to the DCC)

11.7 Unscheduled Assessments for Clinical Events during Follow-Up

Subjects should be instructed to urgently contact study personnel or attend an Emergency Department if they develop symptoms compatible with recurrent VTE or bleeding. These symptoms should be reviewed verbally and also provided to subjects in writing, with relevant contact numbers. Procedures to evaluate suspected clinical events are described in Section 9.

12 PLAN FOR MINIMIZING BIAS

12.1 Justification for Not Using a Double-Blind Design

A double-blind design using sham PCDT procedures will not be used since a) it would be complex and unlikely to achieve effective blinding; b) it could change the efficacy and safety of standard DVT therapy in the Control Arm by causing puncture site bleeding or symptomatic PE; and c) it would cause patient hardship.

12.2 Central Automated Randomization

The use of a centrally-located automated randomization service using a pre-specified randomization schedule with random block sizes prepared by an arms-length statistician will ensure effective concealment of treatment allocation.

12.3 Blinded Outcome Assessments

The following explicit precautions must be taken to minimize the possibility that knowledge of treatment allocation or baseline subject variables will influence outcome assessments:

1. Subjects must be asked not to reveal how they were initially treated when they are seen for scheduled and unscheduled follow-up assessments.
2. Study personnel who perform follow-up assessments must be blinded to subject treatment allocation and must be different than study personnel who initially enroll and treat subjects.
3. Study personnel must not ask subjects about their initial treatment (i.e., if it included PCDT)
4. The conduct and interpretation of outcome assessments (i.e., specific procedures and diagnostic criteria) will be standardized in the study Manual of Procedures.
5. All adjudicators must be blinded to treatment allocation.

Along with effective concealment of allocation, these important precautions will minimize diagnostic suspicion bias, ascertainment bias, and interpretation bias (131-138).

12.4 Avoidance of Crossover

As described in Section 6.2.8, the use of PCDT in Control Arm subjects is strongly discouraged in the absence of limb-threatening circulatory compromise despite anticoagulant therapy. If a Control Arm subject is judged to require PCDT, the Principal Investigator should be notified before PCDT is performed to ensure that this decision is adequately justified and documented. Subjects who crossover will be analyzed in the treatment arm to which they were originally randomized, per the intention-to-treat principle.

12.5 Avoidance of Differential Co-intervention

To minimize the possibility that differing use of standard DVT therapy might influence PTS rates, the following precautions must be taken: (a) bilateral below-knee elastic compression stockings (30-40 mmHg, the same brand to all subjects in each Center) should be used in all subjects (3,31); (b) the recommended intensity (target INR 2.0 to 3.0) and duration of anticoagulant therapy should be the same in both treatment groups (Section 6.1.2) (30). Data pertaining to the actual duration of anticoagulant therapy given and the percent of time spent in the therapeutic range (from INR blood testing) will be compared between the two arms; and (c) criteria for IVC filter use during follow-up will be the same in both arms, and data on filter use will be collected.

12.6 Equal Surveillance of Both Treatment Arms

As subjects in both treatment Arms will receive the same standard DVT therapy and follow-up, the intensity of surveillance will not differ between them.

12.7 Subject Retention, Withdrawal, and Termination

These measures will be taken to promote continued participation of subjects in both Arms:

a) frequent telephone contact using a standardized schedule;
b) electronic facilitation of follow-up (Section 14.3); and
c) reimbursement for travel expenses (Section 18.6.2).

Subjects should be encouraged to remain in the study until follow-up is completed but will be informed that they have the right to withdraw from the study at any time without compromise to their subsequent care. Subjects will be terminated from the study if they die or elect to withdraw. If subjects elect to withdraw, they should be asked for permission for the following:

a) to be visited in their home by study personnel (if feasible);
b) to be contacted by telephone;
c) to have their physicians contacted.

13 REPORTING OF ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

13.1 Definitions

13.1.1 Adverse Event (AE)

An Adverse Event is any untoward medical occurrence observed in a patient that develops or worsens from baseline status in association with a subject's participation in the research, whether considered research-related or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the research, whether or not considered related to the research.

13.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event is any AE that results in one of the following outcomes:

- Death
- A life-threatening adverse experience
- A persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital anomaly, birth defect, or cancer in a neonate/infant born to a female subject
- Pregnancy abortion (accidental, therapeutic, or spontaneous)

Medical events that do not strictly fulfill these criteria may be considered SAEs if they seriously jeopardize the subject or require aggressive intervention to prevent one of these outcomes.

13.1.3 Unanticipated Problem (UP)

An Unanticipated Problem is defined as being any incident, experience, or outcome that meets **all** of the following criteria: 1) it is unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document, and the characteristics of the subject population being studied; 2) it is related or possibly related to participation in the research (meaning that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and 3) it suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (note: per OHRP guidelines, any AE that is serious (i.e. a SAE), unexpected, and related or possibly related to participation in the research automatically meets this third criterion.

13.2 General AE Recording and Reporting Guidelines

13.2.1 Documentation of Adverse Events

AEs should be solicited at all follow-up visits. Subjects should be encouraged to report AEs spontaneously or in response to non-directed questioning (e.g. “How has your health been since the last visit?”). If it is determined that an AE occurred, the Clinical Center investigator should determine if the event fulfills the criteria below for required reporting of the AE to the DCC. If so, obtain all the information needed to complete the electronic Adverse Events CRF. All reportable AEs must be recorded on the Adverse Events CRF and submitted to the DCC using the ATTRACT Trial’s Web-based electronic data capture system. The required reporting

periods for SAEs and non-serious AEs are specified in protocol Sections 13.4 and 13.5, respectively.

13.2.2 Routine Occurrences in DVT Patients

The following occurrences that commonly arise as a result of DVT and its routine clinical care should not be reported as AEs: a) fluctuations in INR and PTT values, unless associated with a bleeding episode (which would be reported as the AE), medical treatment (e.g. Vitamin K administration), or permanent discontinuation of the Study Drug; b) lower extremity symptoms (e.g. leg pain, swelling, fatigue, heaviness) that are clearly due to the initial DVT episode or PTS and that do not merit investigation for recurrent DVT in the physician's judgment (if ultrasound, D-dimer, or other testing/imaging is performed to evaluate for recurrent DVT, the event should be reported as an AE); and c) hospitalizations for the sole purpose of enabling provision of anticoagulant therapy or patient education in the administration of anticoagulant therapy.

13.2.3 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported in the baseline medical/surgical history. A pre-existing medical condition should be re-assessed during the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens significantly or unexpectedly during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g. "more frequent" headaches). Previously scheduled hospitalizations and hospitalizations needed for diagnostic or elective surgical procedures for the management of pre-existing medical conditions are not considered AEs.

13.2.4 Specific Reporting Guidelines

To improve the quality/precision of AE reporting, investigators should follow these guidelines:

1. Use recognized medical terms. Avoid the use of colloquialisms and/or abbreviations.
2. Diagnosis vs. Signs/Symptoms: If known at the time of reporting, a diagnosis should be reported instead of individual signs and symptoms (e.g. record only "hepatitis" rather than jaundice and elevated transaminases). However, if the known signs and symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, the information that is currently available should be reported. If a diagnosis is subsequently established, it should be reported as follow-up information as described in Section 13.5.
3. A cascade of events (i.e. sequelae) should be identified by the primary, causative event. For SAEs, the event cascade can be detailed on the CRF. For example, when recording a

death, the event or condition that caused or contributed to the fatal outcome should be reported as the SAE (death would be the outcome of that SAE). If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

4. Hospitalizations for Medical and Surgical Procedures: Any AE that results in inpatient hospitalization or prolonged of inpatient hospitalization should be reported as a SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure (not the procedure itself) should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery as a result of an AE, record the heart condition that necessitated the bypass as the SAE.

13.2.5 Follow-Up Information

Additional information may be added to a previously submitted report and sent to the CCC and DCC at any time. Subject identifiers, protocol description and number, a brief AE description, and a notation that additional information is being submitted should be included. Occasionally, the Principal Investigator may contact the site investigators for additional information, clarification, or an update on the current clinical status of subjects for whom AEs were reported.

13.3 Categorization of Adverse Events

All AEs must be characterized by the following criteria:

13.3.1 Intensity or Severity

The following categories of the intensity of an adverse event should be used:

Mild	Awareness of a sign or symptom that does not interfere with the patient’s usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the patient’s usual activity, but he/she is still able to function.
Severe	Interrupts a patient’s usual daily activity and generally requires a systemic drug therapy or other treatment

13.3.2 Expectedness

Each AE should be evaluated as to whether it was expected or unexpected. An unexpected AE is defined as any AE the nature, severity, or frequency of which is **not** consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol (e.g. Section 18.3 of this protocol), any applicable investigator brochure, and the current IRB-approved informed consent document; and b) other relevant

sources of information, such as product labeling and package inserts; or

2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

AEs that do not meet the above criteria of an unexpected AE should be graded as expected.

13.3.3 Relatedness to Participation in the Research Study (per OHRP Guidelines)

Each AE should be evaluated as to whether it was related or possibly related to participation in the research study (meaning that there is a reasonable possibility that the AE may have been caused by the procedures involved in the research). AEs determined to be solely caused by an underlying disease, disorder, or condition of the subject; or other circumstances unrelated to the research should be categorized as being not related to participation in the research.

13.3.4 Relatedness to Use of the Study Drug (for FDA Reporting)

Each AE should also be evaluated as to whether it was related to use of the study drug (rt-PA):

Definite	An AE is clearly related to use of the study drug (rt-PA).
Probable	An AE has a strong temporal relationship to use of the study drug (rt-PA), and another etiology is significantly less likely
Possible	An AE has a strong temporal relationship to use of the study drug (rt-PA), and an alternative etiology is equally or less likely.
Unlikely	An AE has little or no temporal relationship to use of the study drug (rt-PA), and/or a more likely alternative etiology exists.
Not Related	An AE is not related to use of the study drug (rt-PA) (no temporal relationship, or a much more likely alternative etiology exists).

Adverse events with rt-PA are well-described and consist mainly of bleeding complications, including major and intracranial hemorrhage (see Section 1.5, Section 1.6, and Section 18.3). The incidence of these complications has been quantified in subjects receiving comparatively large rt-PA doses for acute myocardial infarction, stroke, and PE. Any bleeding that is attributable to rt-PA is most likely to occur within 24 hours of treatment and is very unlikely to occur after 72 hours. Hence, in Experimental Arm subjects, all bleeding events that occur within 72 hours of PCDT initiation will be attributed to the use of rt-PA.

13.3.5 Outcome

The clinical course of all AEs should be followed until a medical outcome is determined (resolution, stabilization, or determination that it was unrelated to study participation). If a

subject becomes pregnant within 90 days of receiving rt-PA, follow-up should be obtained to establish the pregnancy's outcome. The clinical outcome of all AEs will be recorded as follows:

Death	
Recovered	Patient returned to baseline status.
Not Yet Recovered	Patient did not recover and symptoms/sequelae continue.
Recovered with Sequelae	Patient recovered but with clinical sequelae from the event.

13.3.6 Treatment or Action Taken

AEs and SAEs will be categorized by the actions taken in response to the event:

Intervention	Surgery or other invasive procedure
Non-surgical Treatment	Drug initiation, interruption, dose reduction, or discontinuation
None	No action was taken.

13.4 Reporting Requirements for Serious Adverse Events

All observed or volunteered SAEs occurring from randomization through 24 months following randomization, regardless of treatment group or suspected causal relationship to the research study, must be recorded on the designated Serious Adverse Event CRF and submitted to the DCC. The Clinical Center investigator should also report any SAE occurring after a subject has completed or discontinued study participation if it was possibly related to prior rt-PA exposure.

If the investigator should become aware of the development of cancer or congenital anomaly in a subsequently conceived offspring of a female subject, this should be reported as a SAE. The Clinical Center investigators must use the following procedure for reporting SAEs:

1. Report any SAE that occurs within 24 months after randomization to the ATTRACT Trial Clinical Coordinating Center (CCC) at the Washington University School of Medicine. A description of the event should be reported on the electronic Serious Adverse Event CRF and e-mailed or faxed **within 24 hours of knowledge of the event** (Monday-Friday) to:

Suresh Vedantham, M.D.
Principal Investigator, ATTRACT Trial
Mallinckrodt Institute of Radiology
510 S. Kingshighway, Box 8131
St. Louis, MO 63110
Telephone: (314) 362-2923
Fax: (314) 747-1944

E-Mail: vedanthams@mir.wustl.edu

2. Report the SAE to the Clinical Center's local IRB per its regulations. If the event causes death or is life-threatening, this must be done **within 24 hours of knowledge of the event**.
3. Electronically transmit the Serious Adverse Event CRF to the Data Coordinating Center.
4. In reporting SAEs, the investigator should provide any potentially relevant information on subject demographics; pre-existing conditions; the event's description; its date/time of onset, severity, and treatment; results of diagnostic testing; the duration of sequelae; and outcome if known. Information on suspect medications including dose, route of administration, frequency, dates, lot number, expiration date, and concomitant medications should be given.
5. Deaths: Any report of a patient death should be accompanied by a Death CRF, a Follow-Up CRF, an End of Study CRF, an Adverse Event CRF, a Serious Adverse Event CRF, a statement of the pertinent details, and the death records/certificate and autopsy report (if performed). When reporting a death, the primary event or condition that caused or contributed to the fatal outcome should be reported as the SAE (death is the outcome of that SAE). If the cause of death is unknown at the time of reporting, report "Unexplained Death".

At the CCC, Dr. Vedantham (the ATTRACT Trial Principal Investigator and IND Holder) will review the SAE report and obtain any needed additional clarifications concerning the event by direct telephone conversations and/or e-mail with the Clinical Center investigator(s). The Clinical Center investigator's description and categorization of the SAE per the criteria in Section 13.3, and any additional relevant information, will then be reviewed at the CCC by the ATTRACT Trial Safety Officer. The Safety Officer will determine if the SAE was properly categorized. If not, he will provide Dr. Vedantham and the Clinical Center investigator with a modified categorization, along with a brief written rationale for re-categorizing the SAE. In nearly all instances, the Safety Officer's categorization will be considered the CCC's final categorization of the SAE. However, if a Clinical Center investigator continues to believe that a SAE was unexpected or possibly, probably, or definitely related to use of rt-PA, then the event will be reported as such.

13.4.1 Expedited Reporting of SAE that are Unanticipated Problems

The CCC will evaluate each SAE to determine if it fulfills the criteria for being a UP (see Section 13.1.3). Dr. Vedantham (Principal Investigator and IND Holder) will notify the NHLBI Project Officer; the DSMB Executive Secretary; the Washington University Human Research Protection Office; the FDA (fax (800) FDA-1078); Genentech Drug Safety (telephone (650) 225-2232, fax (650) 225-4630 or (650) 225-5288); the ATTRACT Steering Committee, and the Clinical Center

investigators of any SAE that is a UP **within 7 calendar days** of first learning of the event. The Clinical Center investigators are then responsible for notifying their respective IRBs of the UP.

13.4.2 IND Safety Reports

Dr. Vedantham is the Primary Medical Monitor and is responsible for timely submission of the Medwatch 3500a form to the FDA. **Within 15 calendar days** after initial knowledge of any SAE categorized as unexpected and possibly, probably or definitely related to the use of rt-PA, Dr. Vedantham will send a written IND Safety Report to (a) the FDA (faxed to (800) FDA-1078); (b) Genentech Drug Safety fax (650) 225-4630 or (650) 225-5288); (c) the NHLBI Project Officer; (d) the Washington University Human Research Protection Office; (e) the DSMB Executive Secretary; (f) the ATTRACT Steering Committee; and (g) the Clinical Center investigators. This Report will include an Analysis of Similar Events, per 21 CFR 312.32. The Clinical Center investigators are then responsible for providing this Report to their IRBs.

We expect that this strategy will allow the identification of serious or systematic hazards in a timely fashion, facilitating corrective action and appropriate reporting to regulatory agencies.

Contact numbers for Dr. Vedantham (ATTRACT Trial Principal Investigator, IND Holder, and Primary Medical Monitor) and Dr. James R. Duncan (ATTRACT Trial Safety Officer) are below:

Primary Medical Monitor

Suresh Vedantham, M.D.
Principal Investigator, ATTRACT Trial
Mallinckrodt Institute of Radiology
510 S. Kingshighway, Box 8131
St. Louis, MO 63110
Telephone: (314) 362-2923
Fax: (314) 362-2276
E-Mail: vedanthams@mir.wustl.edu

ATTRACT Trial Safety Officer

James R. Duncan, M.D., Ph.D.
Safety Officer, ATTRACT Trial
Mallinckrodt Institute of Radiology
510 S. Kingshighway, Box 8131
St. Louis, MO 63110
Telephone: (314) 747-6281
Fax: (314) 362-2276
E-Mail: duncanj@mir.wustl.edu

For questions regarding AE or SAE reporting, the Clinical Center investigators may contact Dr. Vedantham or the Genentech Medical Science Liaison (Kathy Harbour, Ph.D., telephone (415) 218-4623, fax (949) 706-2464) at any time. Information on all SAEs, any pregnancy that occurs within 3 months of rt-PA use in female subjects (including follow-up on the pregnancy's outcome), all annual reports to the FDA, the final Clinical Study report, and any literature articles that result from the ATTRACT Trial will be copied to the Genentech Medical Science Liaison.

13.5 Reporting Requirements for Non-Serious AEs

All non-serious AEs that occur from randomization through 30 days after randomization, or that occur within 30 days after a PCDT procedure that is performed at any time during the follow-up period, must be reported to the DCC on the Adverse Events CRF. Note: if recurrent VTE or bleeding occurs beyond 30 days but the event does not meet the Section 13.1.1 criteria for a SAE, the event should not be reported to the DCC as an AE. However, the event must still be reported to the DCC as a possible outcome event - a Suspected VTE or Suspected Bleeding CRF would need to be submitted to the DCC along with any relevant source documentation.

13.6 Reporting Requirements for Unanticipated Problems that are not SAEs

Any UP (whether or not it causes an AE) should be reported to Dr. Vedantham by e-mail or fax within 24 hours of knowledge of the event or problem (Monday-Friday), and should also be reported to the site's local IRB per its regulations. For further information on UP reporting, please see the policy at http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm or **Appendix 15**.

The CCC will report any UP along with a description of any corrective action planned or taken in response to the UP to the NHLBI Project Officer, the DSMB Executive Secretary, the FDA, the Washington University Human Research Protection Office, the ATTRACT Steering Committee, Genentech Drug Safety, and the Clinical Center investigators within 30 calendar days (or within 7 calendar days if the UP is fatal, life-threatening, or serious). The Clinical Center investigators are then responsible to notify their local IRBs of any UP of which they are notified by the CCC.

14 DATA REPORTING, PROCESSING AND QUALITY CONTROL

14.1 Training of Field Personnel and Standardization of Assessments

14.1.1 Clinical Outcomes

Before starting the study, all study nurses will complete standardized training on the proper acquisition and reporting of data. This will be accomplished with: a) the Manual of Procedures; b) a start-up Investigator's Meeting with hands-on training and practice sessions using the measurement scales; c) use of a full color, plasticized graphic visual aid for grading signs of PTS using Villalta PTS Scale; d) use of published tables/descriptions that instruct examiners on use of Basic CEAP and the VCSS system, and; e) an on-line training module for the electronic remote data capture system. Administration of the PTS instruments is detailed in Section 8.9.

14.1.2 Imaging Outcomes (Ultrasonography and Venography)

The following steps will be taken to ensure optimal acquisition and quality, standardization, and interpretation of imaging studies: 1) close communication between the Data Coordinating

Center, Clinical Centers, Ultrasound Core Laboratory, and Clinical Coordinating Center in the development of training, operations, and adjudication manuals, aids (including DVDs), and case report forms; 2) diligent credentialing of Ultrasound Substudy Center sonographers (they will have recognized certifications for trained vascular technologists and significant experience with performance of venous Duplex ultrasound exams), vascular ultrasound laboratories (accreditation by American College of Radiology or Intersocietal Commission for Accreditation of Vascular Laboratories), the endovascular physicians (subspecialty board certification), and the Clinical Centers (accredited by the Joint Commission on the Accreditation of Healthcare Organizations); 3) use of high quality venous Duplex ultrasound and digital venography; 4) training sessions for ultrasonography personnel at the yearly Investigator Meetings; 5) certification of individual sonographers by the Ultrasound Core Laboratory based on review of at least 2 random venous Duplex ultrasound examinations performed using the ATTRACT Duplex protocol (**Appendix 12**); 6) independent central interpretation of ultrasound (Ultrasound Core Laboratory) and venogram (DCC) examinations by 2 blinded expert readers, with involvement of a third reader to resolve discrepancies; and 7) ongoing quality control feedback to the Clinical Centers from the central reading facilities at the DCC and Ultrasound Core Laboratory.

14.2 Data Acquisition, Monitoring and Quality Control

Subject data will be collected via a remote-entry web-based Electronic Data Capture (EDC) application. This system utilizes Microsoft's ASP.NET AJAX technology as a method of client-server communication and uses Microsoft SQL 2008 R2 server as the database engine. All data exchange is encrypted using the Secure Sockets Layer (SSL) communication protocol. Application level security is a role-based security model. This system incorporates on-line controls and validation, and web-based query generation and response options. Where appropriate, the database will only accept data within pre-defined ranges, verify that entered dates are consistent for individual subjects, force entry of compulsory fields that must be completed before subsequent data entry, and cross-reference data to check for internal consistency. Entered data that is inconsistent, missing, or erroneous will be flagged for review by DCC staff; if these concerns cannot be resolved with certainty within the Web-based system, DCC staff will contact the Clinical Center for clarification. As a backup, PDF versions of the Case Report Forms will be available on the study website, and completed forms can be faxed to the DCC. At regular intervals, the data will be scrutinized using pre-specified and pre-programmed logic rules to detect outlier values and inconsistent data items. These will be flagged and checked for validity to ensure that reporting or data entry errors have not occurred.

This will be repeated one last time at the completion of the study, but before database lock. In addition to a daily tape backup, databases will be backed-up weekly onto DVDs that are stored in a secure off-site location with restricted access.

14.3 Electronic Facilitation of Follow-Up

The DCC will automatically generate a complete 24-month follow-up schedule for each subject that will be accessible to the Clinical Center within 2 business days of randomization. There will be continuous monitoring of visit completion and the Clinical Centers will be contacted if reporting has not occurred within 7 days of a scheduled visit. If this does not elicit a response or a completed report within 7 days, an electronic reminder will be sent to the Center. If there is no completed report within a further 7 days, the Clinical Center research coordinator, Clinical Center investigator, and ATTRACT Clinical Coordinating Center will be informed of the reporting deficit. This process is expected to achieve timely reporting of nearly all scheduled visits.

14.4 Data Confidentiality

14.4.1 At the Data Coordinating Center

1. Personal identifiers (e.g., name, address, telephone numbers) will not be entered in the electronic database (this data will be stored in a secure location in the Clinical Centers with restricted access) and will be removed from all patient material sent to the DCC for clinical outcomes adjudication (e.g., clinic notes, x-rays). Centers that are unable to de-identify imaging exams may submit the exams provided that doing so is consistent with the signed informed consent form and HIPAA Authorization approved by the local IRB.
2. Clinical Centers will require a complex password to gain access to Web-based documents.
3. The DCC database will be password protected with strong encryption and will incorporate various fire walls and isolated networks.
4. All attempts to access the DCC database will be logged.
5. All data will be destroyed after 25 years.
6. All DCC practices will comply with McMaster University and Hamilton Health Sciences joint policy “Standard Operating Procedures for Clinical Research” and applicable OCOG SOPs related to DCC activities.

14.4.2 At the Clinical Centers, Clinical Coordinating Center, and Core Laboratories

Subject data will be kept in a locked office and on password-protected and firewall-protected computer systems, and will only be available to the research team. Different password-

protected files will be created and will be linked using the participant's unique identification number. Subject names and other personal information will be kept separate from study data. Identifier keys will be stored in separate files which only the site principal investigator and authorized personnel at the site, CCC, or core laboratory can access. A list of names of all personnel who are approved to have such access will be maintained at each Clinical Center.

14.5 Compliance with Laws and Regulations

This study will be conducted in accordance with current FDA Good Clinical Practices, the Health Insurance Portability and Accountability Act (HIPAA), and local ethical and legal requirements.

15 STATISTICAL METHODS

15.1 Sample Size Calculation

The goal of the ATTRACT Trial is to determine if adjunctive PCDT (Experimental Arm), compared with optimal standard DVT therapy alone (Control Arm), reduces the 2-year occurrence of PTS in subjects with symptomatic proximal DVT. Based on previous studies (2-5), 30% of subjects in the Control Arm are expected to have PTS within 24 months of DVT diagnosis. Based on the expected success of PCDT at restoring venous patency and reductions of PTS that were achieved with thrombolytic therapy in earlier studies (33,34,42,51,52,139), we hypothesize that PCDT will reduce the risk of PTS by at least 33%. Accepting a 5% chance of incorrectly concluding that there is a difference in the proportion of subjects with PTS at 24 months with PCDT (α error=0.05; two-sided), and the requirement that the study has an 80% chance (β error=0.2) of detecting a true difference if PCDT truly reduces PTS by 33%, 311 subjects in each group must be studied (based on the Fisher's exact test).

In recently completed studies of long-term treatment for unprovoked VTE coordinated by the DCC, loss to follow-up or death occurred in 2.5% during 2 years follow-up (140), and in 3.4% during mean follow-up of 2.4 years (141). We therefore expect no more than 5% of randomized subjects to be lost to follow-up at 24 months. However, to ensure that statistical power will not be compromised, we will assume that as many as 10% of randomized subjects (double the maximum expected) will not complete the 24-month assessment. Therefore, we plan to randomize 346 subjects to each group, yielding a total study sample size of **692 subjects**.

For the secondary analyses, 692 subjects will provide approximately 88% power to detect an effect size of 0.25 with continuous outcomes. QOL changes from baseline: This translates into the ability to detect a difference of 1.25 in the VEINES-QOL change scores, and 2.5 in the SF-36v2 PCS and MCS change scores (change of 4 points is clinically important for all 3 scales).

PTS severity on Villalta PTS Scale: A difference as small as 1.25 units can be detected (5-point gradations define severity categories) (98, 111). Ultrasound outcomes: Assuming a 50% risk of deep venous reflux in the Control Arm and 10% inflation for losses due to withdrawal, death, or inadequate exams (rare), 142 subjects will provide 80% power to detect a 50% relative risk reduction for this outcome (alpha = 0.05, two-sided). 128 evaluable subjects will provide 80% power to detect effect sizes of 0.5 for reflux and obstruction on the continuous VSDS scales.

Regarding safety, we will perform a descriptive analysis of the rates of major bleeding and symptomatic PE in the two study Arms. These events are expected to occur infrequently (2% for major bleeding at 10 days and for symptomatic PE at 3 months) in the Control Arm. With 311 evaluable subjects per arm, if 2% of each group experiences an outcome, the 95% confidence interval on the difference of 0% will include an absolute decrease or increase of 2.4%.

15.2 Primary Analysis

The primary efficacy analysis is a comparison of the proportion of subjects in each Arm who have developed PTS, defined as a total score of $\geq$ 5 in the limb ipsilateral to the index DVT on the Villalta PTS Scale (or an ulcer) at the 6-month follow-up visit, or subsequently during the 24 months after randomization. A stratum-adjusted Cochran-Mantel-Haenszel test will be used. All testing will be two-sided, and a p-value of 0.05 or less will be considered statistically significant.

Subjects will also be counted as having PTS if they underwent an unplanned endovascular intervention (PCDT or another intervention) for the treatment of severe symptomatic venous disease in the index leg more than 6 months after randomization and either a) they had a total score of $\geq$ 5 on the Villalta PTS Scale that was performed immediately preceding that intervention, or an ulcer; or b) the Villalta PTS Scale was not performed at that time.

Irrespective of any subsequent post-randomization intervention, all patients will be counted in the treatment arm to which they were originally randomized, per the intention-to-treat principle.

Two data sets will be considered:

15.2.1 Modified Full Analysis Set

The modified full analysis set will consist of all subjects randomized except those who did not have DVT (i.e. violated the inclusion criterion) and those deemed to be not analyzable for that outcome. The Adjudication Committee, without knowledge of treatment allocation, will decide if subjects qualify as valid post-randomization exclusions. For subjects who died, were lost to follow-up, or withdrew consent (i.e. refused to be contacted directly or indirectly) before the 24-

month PTS assessment, (142,143), a number of imputation strategies (Section 15.4.2) will be employed in the sensitivity analysis.

15.2.2 Per-Protocol Set

The per-protocol set includes everyone in the modified full analysis set except for any subjects who meet either of the following criteria: (1) randomized to PCDT but did not have skin puncture for endovascular DVT therapy during the first 7 days post-randomization; or (2) randomized to the Control Arm but had skin puncture for PCDT or endovascular DVT therapy, and/or either systemic or local thrombolytic therapy, during the first 7 days post-randomization.

15.3 Secondary Analyses

Secondary analyses will be performed using both analysis sets. To account for multiple testing, a two-sided p-value of 0.01 or less will be considered statistically significant for all tests (144).

15.3.1 Symptomatic Venous Thromboembolism

The proportion of subjects who develop symptomatic VTE within 24 months post-randomization (subdivided according to whether the event was within the first 10 days, 11 to 30 days, 31 to 90 days, or 91 days to 24 months) will be compared between the two treatment groups using a stratum-adjusted Cochran-Mantel-Haenszel test.

15.3.2 Major and Any Bleeding

The proportion of subjects with major bleeding during the 10 days after randomization, and between 11 days and 24 months, will be compared between the two groups using a stratum-adjusted Cochran-Mantel-Haenszel test. A similar comparison will be undertaken for any bleeding (major or minor). The nature of major bleeds (e.g. intracranial, needing surgery or transfusion) will be described. Complications will also be described by outcome according to SIR reporting standards (48,120).

15.3.3 Deaths

Overall and cause-specific counts of death will be described in the two treatment groups; the overall mortality at 1 month and 24 months will be compared using a stratum-adjusted Cochran-Mantel-Haenszel test. In addition, Kaplan-Meier curves will be estimated for the two treatment arms.

15.3.4 Disease-Specific Quality of Life

The change in VEINES-QOL and VEINES-Sym scores from baseline to 24 months will be compared between the two groups using a Student's t-test (for each scale, a difference of 4

points is clinically meaningful). A linear mixed model analysis of the repeated assessments (at 1, 6, 12, 18 and 24 months) with baseline scores as a covariate will be used to investigate the changes over time, and if they differ by treatment arm.

15.3.5 Generic Quality of Life

The change in SF-36v2 PCS and MCS scores from baseline to 24 months will be compared between the two groups using a Student's t-test. A difference of 5 points on each scale is considered to be clinically relevant. In addition, a linear mixed model analysis of the repeated assessments (at 1, 6, 12, 18 and 24 months) with baseline scores as a covariate will be used to investigate the changes over time, and if they differ by treatment arm.

15.3.6 Severity of Post-Thrombotic Syndrome

Villalta severity classification (none, mild, moderate, severe) at 24 months will be compared between the two arms (4 x 2 table) using an exact Kruskal-Wallis nonparametric test with severity as a single ordered factor. In addition, ordinal logistic regression analysis adjusting for baseline factors will be performed. We will also use a linear mixed model for the repeated total Villalta scores (assessed at 10 days and 1, 6, 12, 18, and 24 months) with the baseline score serving as a covariate, to investigate their response patterns over time, and assess if they differ by treatment arm. In addition, the proportion of patients with either moderate or severe PTS will be compared between the two treatment groups using a stratum-adjusted Cochran-Mantel-Haenszel test. The CEAP Clinical Class and VCSS scores will be similarly analyzed.

15.3.7 Major Non-PTS Treatment Failure and Composite Outcome

The proportion of subjects who experience a major non-PTS treatment failure, defined as meeting one or more of the following criteria, will be reported for the two treatment arms:

(1) the subject undergoes an unplanned endovascular or surgical intervention for the treatment of severe symptomatic venous disease in the index leg within the first 6 months after randomization (excluding PCDT Arm patients who undergo repeat PCDT within the first 3 months after randomization, and Control Arm patients whose intervention occurs within 7 days post-randomization and was not prompted by acute limb-threatening circulatory compromise);
(2) the subject undergoes an amputation in the index leg anytime within 24 months after randomization; and/or
(3) the subject develops venous gangrene in the index leg within the first 6 months after randomization.

The composite sum of the proportions of subjects who either develop PTS or experience a major non-PTS treatment failure during 24 months of follow-up will be compared between the two treatment arms using a stratum-adjusted Cochran-Mantel-Haenszel test.

15.3.8 Inter-Relationship between Scales

The relationships between VEINES-QOL, SF-36v2 PCS and MCS scores, Villalta score, CEAP, and VCSS will be explored using multivariate methods.

15.3.9 Residual Thrombosis after PCDT Correlated with PTS

Among Experimental Arm subjects, the extent of proximal DVT on venography after PCDT will be correlated with the presence of PTS at 24 months. For these analyses, extent of residual DVT will be considered as a continuous variable (Marder Score of 0 to 24) and PTS will be considered both as a continuous variable (Villalta score 0-33), and as a dichotomous variable (PTS present or absent). Analysis will include multivariable linear regression for the continuous outcome, and logistic regression for the binary outcome, adjusting for baseline variables.

15.3.10 Residual Thrombosis and Valvular Reflux Correlated with PTS

The extent of residual thrombosis (0-10) and venous reflux (0-10), and the total Venous Segmental Disease Score (0-20), will be described for the two groups, and will be compared (Student's t-test). These scores (total, and component parts) will be correlated with the presence and severity of PTS at 24 months using the techniques outlined in Section 15.3.8.

15.3.11 Resolution of Acute Symptoms

Mean absolute change in severity of leg pain, measured using a 7-point Likert scale, from baseline to 10 days and 1 month after randomization will be compared between the two arms using an analysis of co-variance. Leg circumference (measured and percentage change in leg circumference compared to pretreatment values), at 10 days and 1 month will be compared between the two arms using the Student's t-test. In the PCDT group, the mean change scores in leg pain and leg circumference will be correlated with degree of thrombus removal as assessed by mean change in Marder scores between pre-PCDT and post-PCDT venograms.

15.3.12 Predictors of Therapeutic Response

Exploratory analysis, using linear regression and logistic regression models, will be performed to identify baseline variables associated with reduced PTS. Within the PCDT group, differences in endovascular technique will be described and associations with outcomes will be explored. A history of previous ipsilateral DVT and any previous DVT will be included as analysis variables.

15.4 Additional Analysis Issues

15.4.1 Confounding

Stratification at randomization for the extent of DVT and Clinical Center and the standardization of the use of standard DVT therapy (Section 12.5) will reduce the potential for confounding. However, in addition to the unadjusted analysis described above, an adjusted analysis of the study outcomes comparing treatment Arms will be performed using multivariable regression analysis (linear regression for continuous outcomes, logistic regression for binary outcomes) that controls for the following baseline variables as main effects: age (continuous), gender (female vs. male), ethnicity (Hispanic/Latino vs. other), race (American Indian/Alaskan Native, Asian, Black, Hawaiian/Pacific Islander vs. White), body-mass index, employment status, previous ipsilateral DVT, inpatient (yes, no), duration of leg symptoms, extent of DVT at presentation (iliofemoral vs. femoropopliteal), symptom severity at presentation, and Clinical Center.

15.4.2 Missing Data

The training of study personnel, the use of electronic Case Report Forms that have been pilot tested for clarity, and the precautions noted in Section 14.3 are expected to minimize the occurrence of missing data. If a subject misses a visit but can be reached by phone within 1 month of the visit, the five patient-reported symptom questions of Villalta PTS Scale will be asked over the phone. From these responses, the total (symptoms plus signs) Villalta score will be estimated using a simple imputation algorithm. The same algorithm will be used for other situations in which the Villalta PTS assessment is only partially completed. From the data in our recently completed study (145), the correlation between the Villalta symptom and total scores was found to be extremely high (between 0.85 and 0.90). Similarly, the VEINES and SF-36v2 questionnaires will also be administered by phone in the rare situations when the subject is unable to attend clinic. For missed visits, the total Villalta score, the SF-36 component scores, and the VEINES Sym and QOL component scores will be estimated using multiple imputation (MI) methods, but only for the sensitivity analysis. For all other outcomes, no missing data imputation will be undertaken. For missing baseline data items that serve as covariates, iterative methods such as the Markov Chain Monte Carlo (MCMC) method will be employed to solve this problem. The possibility of non-ignorable missing outcomes will be investigated in exploratory analyses.

15.4.3 Software

All data checking/manipulation and most of the analysis and graphics will be undertaken using SAS (Cary, NC) software. In addition, Cytel's StatXact software will be used for all exact

nonparametric analysis; the R open-source software will be used for any non-standard statistical analysis and to produce plots; the Minitab (State College, PA) statistical and graphics software will also be used to produce plots. The latest available versions will be used.

15.5 Interim Analyses and Stopping Guidelines

All relevant data and summaries will be provided to the Data Safety Monitoring Board (DSMB) by the DCC (Section 17.4). The DSMB will review the frequency of adverse safety outcomes, particularly symptomatic VTE and major bleeding, at intervals that it determines (146,147). Initially, such reviews will be done without knowledge of allocation, but the DSMB can request unblinding at any stage. Based on an overall assessment of risk and benefit, the DSMB can recommend premature stopping of the study to the NHLBI at any time.

We do not anticipate early stopping because of superior efficacy of PCDT because: (1) the primary outcome for efficacy reflects symptoms rather than survival; and (2) it is most improbable that evidence of superior efficacy of PCDT of a sufficient size to change clinical practice can be obtained without enrollment of nearly the entire planned sample size (148,149).

15.6 Statistical Analysis Plan

A detailed statistical analysis plan will be prepared by the study statistician and submitted to the Steering Committee and DSMB for review and approval prior to unblinding and database lock.

16 INVESTIGATOR RESPONSIBILITIES

16.1 Study Initiation

Before enrollment of the first subject at each Clinical Center, the following documents must be on file with the ATTRACT Clinical Coordinating Center at Washington University:

- Original U.S. FDA Form 1572, signed by the site principal investigator. The names of all co-investigators at the Clinical Center must also appear on this Form.
- Current curriculum vitae of the principal investigator and all co-investigators.
- Current, dated Institutional Review Board (IRB) membership list.
- Written documentation of IRB protocol approval (protocol number/title and approval date) and informed consent document (protocol number/title and approval date).
- A copy of the IRB-approved informed consent document. The informed consent document must be reviewed by the study Principal Investigator prior to IRB submission.
- A copy of the IRB-approved authorization for Protected Health Information (HIPAA

requirement). This may be integrated into the patient informed consent document.

- Written documentation of IRB review and approval of any advertising materials that will be used for subject recruitment to the study.
- Current laboratory certification (Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists [CAP]) of the institution listed on the Form 1572
- Medical Therapy Committee certification of anticoagulation monitoring plans and medical co-investigator credentials
- Interventions Committee certification of endovascular co-investigator credentials
- Ultrasound Core Laboratory certification to perform compression ultrasound exams

16.2 Study Completion

The following data and materials must be on file at the Clinical Coordinating Center at Washington University before the study can be considered complete or terminated:

- Laboratory findings, clinical data and test results from screening through end of follow-up.
- Case Report Forms, properly completed.
- Copies of protocol amendments and IRB approvals, if appropriate.
- Review of final visit checklist.
- Copy of study termination letter sent to the IRB.
- All regulatory documents (CV for each investigator, U.S. FDA Form 1572 for each Center)

16.3 Institutional Review Board Approval

The protocol, informed consent document, and supporting information must be approved by the IRB before study initiation. The study will be conducted in accordance with the requirements of the FDA, NHLBI, applicable national and local health authorities, and participating institutions' IRBs. The Clinical Center principal investigator is responsible for keeping the IRB apprised of study progress and protocol changes as deemed appropriate, at a minimum of once a year. The Clinical Center principal investigator must also notify his/her IRB of all unexpected SAEs. Some IRBs have other AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety update provided by the Principal Investigator (i.e. IND Safety Report, safety amendments, updates to the study protocol).

Changes or additions to the study protocol or informed consent document at a Clinical Center must be approved in writing by the ATTRACT Principal Investigator and the Center's IRB.

16.4 Informed Consent

Template informed consent documents will be provided to each site. The final IRB-approved document must be provided to the study Principal Investigator, including the protocol version and date. The informed consent document must be signed by the subject or his/her legally authorized representative before participation in the study. A copy of the informed consent document must be provided to the subject or his/her legally authorized representative. If applicable, it should be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and be available for verification by Clinical Coordinating Center personnel at any time. Documentation of the date informed consent was obtained and a notation that a signed copy was given to the subject should be recorded. The informed consent process must always be conducted in a non-coercive manner, and should be consistent with the FDA regulation 21CFR, Part 50.

16.5 Study Monitoring Requirements

Site monitoring visits will be routinely conducted by authorized representatives of the Principal Investigator to inspect study data, informed consent forms, subjects' medical records, and Case Report Forms, pursuant to U.S. GCPs and other federal and local regulations. The Clinical Center principal investigator will permit authorized representatives of the FDA, NHLBI, Washington University, and local health authorities to inspect relevant facilities and records.

16.6 Case Report Forms

Web-based electronic CRFs will be provided to the Clinical Centers by the Principal Investigator and DCC. All CRFs should be filled out completely by the study coordinator or investigators. The CRFs must be reviewed by the site investigator prior to submission to the DCC. CRFs should be completed in a neat, legible manner to ensure accurate interpretation of the data.

16.7 Disclosure of Data

Subject information obtained by this study is confidential, and disclosure to parties other than those noted here is prohibited. Upon the subject's permission, medical information may be given to his/her physician or other medical personnel responsible for his/her welfare. Study data must be available for inspection upon request by representatives of the Principal Investigator, FDA, NHLBI, Washington University, and other national and local health authorities.

16.8 Retention of Records

U.S. Department of Health and Human Services (DHHS) Regulations (45 CFR 46.115) mandate that IRB records of the study must be retained for at least 3 years after study completion. In addition, FDA regulations require that records and documents pertaining to the conduct of this study and the distribution of rt-PA, including CRFs, signed informed consent forms, supporting source documentation for values or responses in the CRFs, supporting documentation for AEs, laboratory test results, and medication inventory records, must be retained by the investigator for at least 2 years after the study ends. The CCC and DCC reserve the right to secure data clarification and additional medical documentation on patients enrolled in this trial. To avoid error, the Clinical Center investigator should contact the Clinical Coordinating Center before destroying any records and reports pertaining to the trial to ensure they are no longer needed. The following records should be maintained by the Clinical Center investigator:

- Signed Confidentiality Agreement
- Study Protocol and Protocol Amendments
- Signed Clinical Trial Agreement
- FDA Form 1572 and Investigational Drug Accountability Logs
- IRB Approval Letter, Continuing Review Approval Letters, and Correspondence
- IRB Membership List
- Curriculum vita and licenses for all investigators and research coordinators
- Site Personnel Signature List
- Financial Disclosure/Conflict-of-Interest Forms
- Patient Screening & Enrollment Log
- Laboratory Certifications
- NIH Training Certifications for Responsible Conduct of Research
- Certifications from Ultrasound Core Lab, Interventions Committee, Medical Therapy Committee
- Signed Study Informed Consent Forms for each patient
- All completed eCRFs
- Supporting source documentation for values or responses in eCRFs
- Supporting source documentation for adverse events

17 DATA AND SAFETY MONITORING PLAN

17.1 Role of the Principal Investigator

Dr. Vedantham, the Principal Investigator and IND Holder, will take primary responsibility for monitoring patent safety during the Trial: (a) Dr. Vedantham will lead weekly meetings with CCC personnel to discuss protocol adherence (and any violations), review all SAEs, verify that these events were appropriately reported and examined, and institute any needed changes; (b) via bi-monthly Operations Committee conference calls and additional communications as needed, Dr. Vedantham will routinely discuss any safety issues with the DCC Chair and Study Chair. The DCC Chair may audit data relevant to subject safety when needed; and (c) on quarterly conference calls, Dr. Vedantham will update the Steering Committee on any safety issues.

17.2 Monitoring of Trial Safety by ATTRACT Study Personnel

As described in Section 9 and Section 13, during the trial the occurrence of study outcome events, Adverse Events, and Serious Adverse Events will be documented on dedicated eCRFs and forwarded to the DCC on an ongoing basis in a manner consistent with ICH Requirements (ICH Harmonized Tripartite Guideline for Good Clinical Practice May 1996; Clarifying Adverse Drug Events; a Clinician's Guide to terminology, Documentation, and Reporting; Nebeker et al; *Ann Intern Med* 2004;140:795-801). In addition, SAEs will be directly reported by the Clinical Center investigators to the Principal Investigator at the CCC, and to their respective IRBs. As detailed in Section 13, SAEs will be carefully reviewed and categorized by an independent ATTRACT Safety Officer at the CCC, and reported accordingly to the DCC. Expedited reporting of unexpected SAEs to the FDA, NHLBI Project Officer, Genentech Drug Safety, the Washington University Human Studies Committee, the Clinical Center investigators, and the Clinical Center IRBs will also occur. During the trial, the DCC Chair will inform the DSMB Chair (see below) of any new relevant safety information. If there are concerns about the safety or the conduct of the study, the Steering Committee Chair will also be informed.

17.3 Protocol Violations

Site investigators should notify the CCC of suspected protocol violations within 24 hours of becoming aware of them (Monday-Friday). The CCC will rapidly and firmly address any protocol violations. If a protocol violation is detected or suspected, the Clinical Center investigators will first be asked to provide an explanation. After reviewing the available information, the Principal Investigator will categorize protocol violations as either major (eligibility or primary/secondary endpoint determination compromised or indefinite, or potential for causing substantial patient harm) or minor (data still able to be used for endpoint determination), and will record and track

them for each site. For minor violations, a letter or e-mail will be sent to the site investigator and research assistant notifying them of the violation and asking them to explain the violation. If it is evident that the protocol is misunderstood, clarification will be provided. Major protocol violations will generate a letter from the Principal Investigator or Study Chair to the site investigators and research coordinator, informing them of the violation and requesting a written explanation. The ATTRACT Project Manager and, as needed, the Principal Investigator will communicate with the Clinical Center personnel to confirm that a process is in place to ensure that further protocol violations do not recur. If a major protocol violation occurs twice in any site without justification, it will be dropped as an enrollment center. Review of all protocol violations will be a standard component of the weekly CCC team meetings (led by Dr. Vedantham). All major protocol violations will also be reviewed by the Operations Committee.

17.4 Establishment of an Independent Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board has been established for the ATTRACT Trial. The DSMB, an independent external committee which will monitor patient safety and evaluate the intervention's efficacy, will report to the NHLBI. The DSMB's overall responsibility is to protect the safety of study subjects and to provide ongoing, critical, and unbiased evaluation of the study's progress.

The specific responsibilities of the DSMB, membership qualifications, board process, interim reports from the DCC, DSMB reports, and stopping procedures are described in the DSMB Charter, per the NHLBI's Policy for Data and Safety Monitoring.

The DSMB includes members that have complementary expertise in the areas of clinical venous thromboembolism, endovascular interventions, clinical trials methodology, and biostatistics.

18 POTENTIAL RISKS AND BENEFITS

18.1 Potential Benefits to the Subject

The goals of PCDT are to prevent PTS and preserve health-related quality of life. There is no guarantee of benefit to any subject. However, we expect that subjects randomized to PCDT will experience a lower rate of PTS, improved QOL, and faster relief of presenting DVT symptoms.

18.2 Potential Benefits to Society

If PCDT is shown to prevent PTS and improve long-term QOL in the ATTRACT Trial, then this procedure may be offered to many more subjects with proximal DVT, enabling them to have less PTS symptoms, less interference with daily activities, less work disability, and improved QOL. If PCDT is shown to be cost-effective, society may benefit via preservation or more efficient use of

healthcare resources. Given our expectation that the state-of-the-art PCDT methods used in ATTRACT have a better safety profile than previous endovascular therapy methods, the study is expected to show that these important benefits to society can be achieved at acceptable risk to a relatively small number of research subjects.

18.3 Potential Risks to the Subject

18.3.1 Risks of Standard DVT Therapy

The following are risks of standard DVT therapy, irrespective of study participation: Discomfort due to use of elastic compression stockings (likely); transient discomfort/pain (likely), minor bruising/bleeding (likely), infection (less likely), or fainting (less likely) due to blood draws for warfarin monitoring; transient discomfort/pain (likely) or minor bruising (likely) due to LMWH injections; major bleeding needing transfusion (less likely); heparin-induced thrombocytopenia (less likely); fatal or intracranial bleeding (rare); malposition / migration of filters or stents (rare).

18.3.2 Risks of Research Procedures Performed on Subjects in Both Arms

Minor local discomfort due to the pressure of the ultrasound transducer on the skin; transient discomfort/pain (likely), minor bruising or bleeding (likely), infection (less likely), or fainting (less likely) due to an extra blood draw that may be needed for screening; psychological discomfort in completing PTS and QOL questionnaires (less likely); inconvenience at having to return for follow-up visits (likely); loss of confidentiality of medical records or economic data (rare).

18.3.3 Likely Risks of Study Drug or Experimental Therapy (PCDT) Procedures

Anxiety related to undergoing PCDT; discomfort/pain and/or bruising at sites of blood draws, intravenous line placements, and/or venous access sites for deep venous catheter placement.

18.3.4 Less Likely Risks of Study Drug or Experimental Therapy (PCDT) Procedures

Infection or fainting due to intravenous line/catheter placement or additional peripheral blood draws needed to monitor therapy; major bleeding requiring transfusion; nausea, vomiting, and/or allergic reaction to iodinated contrast or other medications; local discomfort during use of thrombectomy devices, angioplasty, or stent placement; transient bradycardia during use of the AngioJet; re-thrombosis of a treated segment which elevates PTS risk; symptomatic PE.

18.3.5 Rare Risks of Study Drug or Experimental Therapy (PCDT) Procedures

Allergic reaction to rt-PA; severe allergic reaction (e.g. anaphylaxis) to iodinated contrast or other medications; fatal, life-threatening, or intracranial bleeding or stroke; severe internal (e.g. gastrointestinal, retroperitoneal) bleeding that requires surgical intervention; fatal or life-threatening PE; radiation injury; device-related trauma to vascular structures (i.e. vein wall or

valves) which elevates the risk of bleeding, re-thrombosis, or PTS; hemolysis resulting in excessive blood loss or renal compromise; or other rare or unknown side effects; death.

18.4 Protection of Subjects against the Risks of Standard DVT Therapy

Medical DVT therapy will be supervised by a board-certified physician who is experienced with management of anticoagulant therapy in DVT patients and who has been credentialed by an expert Medical Therapy Committee. This Committee will also monitor advances in medical DVT therapy – if the standard of care changes during the study, this committee may recommend protocol changes to the Steering Committee to ensure that subjects continue to receive best medical care. Complications of anticoagulation will be minimized by the use of widely accepted UFH and LMWH dosing, diligent laboratory monitoring of UFH and warfarin therapy, and a platelet count at 10 days (to identify HIT). If acute limb-threatening circulatory compromise develops during therapy, subjects can be crossed over to receive PCDT. If symptomatic PE occurs despite therapeutic level anticoagulation, subjects will receive IVC filters or alternative anticoagulant therapy regimens. To aid subjects in maintaining compliance with therapy, elastic compression stockings will be provided to the patient and replaced at regular intervals.

18.5 Protection of Subjects against the Risks of Research Procedures

18.5.1 Before Enrollment

A rigorous screening process will be used to ensure that subjects who are not likely to benefit from PCDT or who are at particularly high risk for adverse outcomes are excluded from the study (Section 4). This will include confirming the imaging diagnosis of DVT (to ensure that patients without DVT are not inadvertently enrolled), performing a detailed history and physical examination (to ensure that enrolled subjects truly fulfill all eligibility criteria, are symptomatic, and are not severely ill), and carefully reviewing the results of laboratory testing (in particular, pregnancy test, hemoglobin level, platelet count, INR level, and estimated glomerular filtration rate). If there is hemodynamic compromise from PE, acute limb-threatening circulatory compromise, or an intracranial lesion of any kind, he/she will not be enrolled in the study.

18.5.2 During PCDT

PCDT procedures will be performed by a board-certified endovascular specialist who is experienced with DVT treatment using PCDT and who has been appropriately credentialed by an expert Interventions Committee. Analgesia and anxiolysis during PCDT procedures will be provided through use of conscious sedation. The risks of conscious sedation will be minimized by continuous monitoring of heart rate, blood pressure, oxygen saturation, and cardiac rhythm during the procedures. Strict sterile technique will be used to prevent infections related to skin

puncture. Discomfort at the venous access site will be minimized by administration of local anesthesia into the overlying skin and tissues. Catheter access into the deep leg veins will be performed using ultrasound-guided puncture to prevent inadvertent arterial punctures with subsequent bleeding. Real-time fluoroscopic monitoring of all catheter/wire manipulations will be used to prevent vascular injury. Automated power injections of contrast for venography will not be permitted, in order to prevent clot embolization. During PCDT procedures, subjects will receive anticoagulation to prevent PE and facilitate clot removal. To prevent immediate re-thrombosis, standard adjunctive measures to remove thrombus (balloon maceration, aspiration thrombectomy, and rheolytic thrombectomy) and correct venous stenosis (angioplasty, stents) may be used at the physician's discretion. To avoid bleeding, the target PTT for UFH therapy during infusion CDT will be less than 2 times control. If bleeding develops, the physician may stop the rt-PA, heparin, and use protamine (to reverse the UFH) or cryoprecipitate if needed.

The risk of significant contrast reactions will be minimized by study participation criteria that exclude subjects with severe allergic reactions from participating in the study. The risk of contrast-related renal dysfunction will be minimized by exclusion of subjects with estimated glomerular filtration rate < 60 ml/min (diabetics) or < 30 ml/min (non-diabetics), use of non-ionic contrast agents, and appropriate pre-procedure hydration. Device-related complications, primarily stent misplacement, migration, mechanical failure, or vascular injury, will be diminished by meticulous angiographic technique. Bleeding risks will be minimized by the use of PCDT (which reduces the amount of rt-PA delivered to the systemic circulation), by limiting the total first-session rt-PA dose to 25mg, by limiting the total infusion duration to 30 hours, and by limiting the total rt-PA dose to a maximum of 35mg. The risk of PE will be reduced via use of retrievable IVC filters in selected subjects deemed to be at high PE risk during PCDT. The risk of clinically-significant hemolysis and bradycardia with the AngioJet will be minimized by exclusion of subjects with moderate (diabetics) or severe (non-diabetics) renal dysfunction and by limitation of the total device activation time and infusate volume. A physician will be present during all PCDT procedures to monitor the subjects and treat adverse events.

18.5.3 During Follow-Up

Changes in health status will be assessed by the study nurse at each follow-up visit – if any medical conditions are identified that warrant evaluation, subjects will be encouraged to contact their primary physician. At each visit, the study nurse will encourage the subject to be compliant with anticoagulant therapy and compression stockings to minimize the risk of PTS and recurrent venous thromboembolism. Subject comfort with the self-completion of QOL questionnaires will

be facilitated by ensuring that study nurses are trained in how to administer them properly. The subject may choose not to answer any question with which he/she is uncomfortable.

18.5.4 Protection against Radiation Risks

The amount of radiation to which subjects undergoing PCDT are exposed is about 650 mrem, which is approximately 13% of the maximum allowable annual effective dose for a radiation worker. We will minimize subject exposure to radiation via tight collimation, use of pulsed fluoroscopy, and judicious image acquisition.

18.5.5 Protection against Loss of Confidentiality

Subject confidentiality will be protected by maintaining all paper records in locked file cabinets in locked offices, and all electronic records in password-protected computer files. Any identifying information will be removed from images or other data used in publication or presentations. All database information will be stored on computer systems that are located behind an electronic firewall, which only permits access to certified users. Access to study data files will be protected by password. Strict adherence to HIPAA guidelines for the protection of PHI will be exercised.

The Clinical Center investigators and their staffs will try to reduce, control, and treat any complications from this research. Subjects are free to contact the site principal investigator, the IRB Chairperson at their site or at Washington University, and/or Dr. Vedantham at any time.

18.6 Costs and Compensation to Subjects

18.6.1 Costs to Subjects

Most of the drugs, tests, and procedures administered are performed as part of routine DVT care. Coverage of these services is subject to the specific coverage requirements of the patient's private insurance, and to local and national Medicare coverage policies. Subjects are responsible to pay any costs which are not reimbursed by their insurance carrier, and are also responsible for any applicable co-payments required by their respective policies. The study drug (rt-PA) and the elastic compression stockings will be donated by their manufacturers at no cost to subjects. In addition, subjects will not be charged for the following costs that are specifically related to conduct of the research study: additional research ultrasounds done at baseline, 1-month, and 1-year follow-up; or follow-up physical exams and leg circumference measurements.

18.6.2 Compensation of Subjects

Subjects will not be paid for their participation in the ATTRACT Trial. However, they will receive up to $100 to compensate them for the time and travel involved in completing the research PTS assessments and quality of life questionnaires ($20 per visit starting at 1-month follow-up visit).

18.7 Minors as Research Subjects

Because PTS can cause health impairment in children (150) and a number of studies suggest that children ≥ 16 years old can be safety treated using adult rt-PA dosing regimens (69,151), children ≥ 16 years old will be included in ATTRACT. Per DHHS guidelines, for subjects who are minors, we will obtain written informed consent from at least one parent and the written assent of the child subject. However, permission will be sought from both parents when it is possible to do so. As for adults, the consent process will take place in a non-coercive manner.

19 STUDY COMMITTEES AND ORGANIZATION

A study organizational chart, with lists of committee members, appears in **Appendix 1**.

19.1 Steering Committee

Chair: Dr. Samuel Z. Goldhaber (Study Chair)

Members: Drs. David Cohen, Anthony Comerota, Heather Gornik, Michael Jaff, Jim Julian, Susan Kahn, Clive Kearon, Stephen Kee (SIR Foundation representative), Andrei Kindzelski (NHLBI Project Officer), Lawrence Lewis, Elizabeth Magnuson, Timothy Murphy, Mahmood Razavi and Suresh Vedantham (Principal Investigator).

Key Responsibilities:

1. serve as the overall governing and advisory body for all phases of study development, execution, analysis, and dissemination of results;
2. review study progress, including enrollment, protocol adherence, and trial design;
3. identify and invite members to serve on ATTRACT committees;
4. review and approve all protocols, training materials, eCRFs, and the Manual of Operations;
5. review monthly reports from the Operations Committee;
6. provide final approval for ancillary study and publication requests.

Reporting:

The Steering Committee will provide regular updates to the NHLBI. The Steering Committee will teleconference every 3 months and will meet face-to-face on an annual basis.

19.2 Operations Committee

Chair: Dr. Suresh Vedantham (Principal Investigator)

Members: Drs. Samuel Z. Goldhaber, Clive Kearon and Timothy Murphy

Key Responsibilities:

1. provide daily operational oversight for the trial;
2. monitor operations at the CCC, DCC, and Core Laboratories to ensure proper coordination;
3. coordinate development of the Manual of Operations; and
4. develop policies for and provide initial review of publication and ancillary study requests.

Reporting:

The Operations Committee will report to the Steering Committee. The Operations Committee will teleconference twice each month and will meet face-to-face on an annual basis.

19.3 Clinical Coordinating Center (Washington University)

Chair: Dr. Suresh Vedantham (Principal Investigator)

Key Responsibilities:

1. monitor the Clinical Centers and be the study's primary communication & coordination hub;
2. oversee Clinical Center selection, enrollment, quality assurance, subject retention, adverse event reporting, regulatory compliance, and protocol adherence at the Clinical Centers;
3. manage the financial aspects of the study;
4. maintain the study Website;
5. produce a monthly newsletter for distribution to the Clinical Centers;
6. maintain a 24-7 contact line for the Clinical Center investigators; and
7. serve as a repository for study-related communications.

Reporting:

The CCC Chair will report to the Operations Committee and will supervise the CCC committees below. Each of these committees will report to the CCC Chair on a monthly basis.

19.3.1 Society of Interventional Radiology (SIR) Foundation

Chair: Dr. Stephen Kee

Key Responsibilities:

1. Maintain an updated database of potential Clinical Centers;
2. Work with the Enrollment Committee to increase national awareness of ATTRACT using the SIR Foundation's public relations resources, media contacts, and CME programs;
3. Contribute expertise to the Steering Committee; and
4. Disseminate the study results when they become available.

Reporting:

The SIR Foundation will report to the CCC chair on a monthly basis.

19.3.2 Enrollment Committee

Chair: Dr. Suresh Vedantham

Key Responsibilities:

1. Assist the Clinical Centers in developing site-specific enrollment plans;
2. Create and implement a plan to increase national trial awareness;
3. Develop written materials for point-of-contact subject recruitment;
4. Review enrollment statistics monthly, ensure proportionate enrollment of women and minorities, periodically assess the characteristics of enrolled subjects to ensure that there is reasonable representation of subject subgroups for which different PCDT outcomes might be expected (e.g. iliofemoral versus femoropopliteal DVT, good popliteal vein inflow versus poor popliteal vein inflow, etc.), and make recommendations to the Operations Committee on how to remedy any identified deficiencies via adjustments in study enrollment protocol.

19.3.3 Interventions Committee

Chair: Dr. Mahmood Razavi

Key Responsibilities:

1. Develop the PCDT protocol sections of the Manual of Operations;
2. Adjudicate PCDT protocol issues;
3. Credential and train the endovascular co-investigators;
4. Monitor endovascular procedure/device performance during the study; and
5. Continuously monitor advances in endovascular care of relevance to the study protocol.

Reporting:

The Interventions Committee Chair will report to the CCC Chair monthly.

19.3.4 Medical Therapy Committee

Chair: Dr. Heather Gornik

Responsibilities:

1. Develop the standard DVT therapy protocol sections of the Manual of Operations;
2. Adjudicate standard DVT therapy protocol issues;
3. Credential and train the medical co-investigators;
4. Monitor use of standard DVT therapy in study subjects; and
5. Continuously monitor advances in medical DVT therapy of relevance to the study protocol.

Reporting:

The Medical Therapy Committee Chair will report to the CCC Chair monthly basis.

19.3.5 Ultrasound Core Laboratory (VasCore at Massachusetts General Hospital)

Chair: Dr. Michael Jaff

Responsibilities:

1. Develop the ultrasound protocol sections of the Manual of Operations;
2. Adjudicate ultrasound protocol issues;
3. Credential and train the Vascular Ultrasound Laboratories and sonographers;
4. Ensure quality control of ultrasound studies;
5. Provide central interpretation of ultrasound studies; and
6. Work closely with the DCC to develop eCRFs and process ultrasound data.

Reporting:

The Ultrasound Core Laboratory Chair will report to the CCC Chair monthly.

19.3.6 Clinical Centers

Each ATTRACT Clinical Center has a motivated, multidisciplinary team with an endovascular co-investigator (responsible for performing PCDT), a medical co-investigator (responsible for supervising standard DVT therapy in subjects), an emergency medicine physician (responsible for identifying potential subjects with DVT), and the Vascular Ultrasound Laboratory Director (responsible for identifying potential subjects with DVT, providing quality performance and reporting of ultrasound exams, and working with the Ultrasound Core Laboratory to ensure proper data collection). All co-investigators attested in writing to clinical equipoise (that randomization to either treatment is appropriate for subjects who meet the eligibility criteria).

19.4 Data Coordinating Center (Ontario Clinical Oncology Group, McMaster University)

Chair: Dr. Clive Kearon

Key Personnel: Drs. Susan Kahn (Clinical Outcomes Committee Chair), Jim Julian (Lead Biostatistician), Mark Levine (Adjudication Committee Chair)

Responsibilities:

1. contribute methodological and biostatistical expertise;
2. develop data capture and quality control methods;
3. develop eCRFs with the CCC and Core Laboratories;
4. develop and securely maintain a study database;
5. implement a standardized process that ensures blinded data collection and minimizes bias;
6. perform blinded adjudication of clinical and venographic outcomes;
7. produce and reconcile site data queries;
8. generate specific study reports as requested by study leadership and the DSMB; and

9. provide oversight over the activities at the Health Economic Core Laboratory.

Reporting:

The DCC Chair will report to the Operations Committee and will supervise the DCC committees and the Health Economic Core Laboratory, as described below.

19.4.1 Clinical Outcomes Committee

Chair: Dr. Susan Kahn

Responsibilities:

1. contribute expertise on the measurement of PTS and QOL and on scoring of the measures;
2. oversee the training of study nurses on use of the PTS and QOL measures.

Reporting:

The Clinical Outcomes Committee Chair will report to the DCC Chair monthly.

19.4.2 Independent Adjudication Committee

Chair: Dr. Mark Levine

Responsibility:

Perform blinded adjudication of clinical and venographic outcomes.

Reporting:

The Adjudication Committee Chair will report to the DCC Chair monthly.

19.4.3 Health Economics Core Laboratory

Chair: Dr. David Cohen

Key Personnel: Dr. Elizabeth Magnuson

Responsibilities:

1. contribute expertise with health economic analysis to the study design;
2. integrate economic data collection into the mainstream activities of each Clinical Center;
3. monitor subject use of cost diaries;
4. directly collect itemized hospital bills and UB92 summary bills; and
5. conduct a cost comparison and estimate the incremental cost-effectiveness of the two treatment strategies.

Reporting:

The Health Economic Core Laboratory Chair will report to the DCC Chair monthly.

20 REFERENCES

1. Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125(1):1-7.
2. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, Bernardi E, Girolami PS, Girolami A. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 1997; 82:423-428.
3. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, Tormene D, Mosena L, Pagnan A, Girolami A. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004; 141:249-256.
4. Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. Int Angiol 2004; 23:206-212.
5. Van Dongen CJJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost 2005; 3:939-942.
6. Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood Rev 2002; 16:155-165.
7. Beyth RJ, Cohen AM, Landefeld S. Long-term outcomes of deep-vein thrombosis. Arch Intern Med 1995; 155:1031-1037.
8. O'Donnell TF Jr., Browse NL, Burnand KG, Thomas ML. The socioeconomic effects of an iliofemoral venous thrombosis. J Surg Res 1977; 22:483-488.
9. Monreal M, Martorell A, Callejas JM, Valls R, Llamazares JF, Lafoz E, Arias A. Venographic assessment of deep vein thrombosis and risk of developing post-thrombotic syndrome: a prospective study. J Intern Med 1993; 233:233-238.
10. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med 2002; 162:1144-1148.
11. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. Ann Surg 2004; 239(1):118-126.
12. Kahn SR, Ducruet T, Lamping DL, Arsenault L, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Johri M, Shrier I. Prospective evaluation of health-related quality of life in patients with deep venous thrombosis. Arch Intern Med 2005; 165:1173-1178.
13. Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, O'Fallon M, Melton LJ III. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. J Vasc Surg 2001; 33:1022-1027.
14. Caprini JA, Botteman MF, Stephens JM, Nadipelli V, Ewing MM, Brandt S, et al. Economic

burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. Value Health 2003; 6(1):59-74.

15. Phillips T, Stanton B, Provan A, Lew R. A study of the impact of leg ulcers on quality of life: financial, social, and psychologic implications. J Am Acad Dermatol 1994; 31:49-53.
16. Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. Ann Intern Med 1997; 126:454-457.
17. Browse NL, Burnand KG. The postphlebitic syndrome: a new look. In: Bergen JJ, Yao JST, eds. Venous problems. Chicago:Year-Book 1978; 395-404.
18. Olin JW, Beusterien KM, Childs MB, Seavey C, McHugh L, Griffiths RI. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. Vasc Med 1999; 4:1-7.
19. Markel A, Manzo RA, Bergelin RO, Strandness DE. Valvular reflux after deep vein thrombosis: incidence and time of occurrence. J Vasc Surg 1992; 15:377-384.
20. Caps MT, Manzo RA, Bergelin RO, Meissner MH, Strandness DE. Venous valvular reflux in veins not involved at the time of acute deep vein thrombosis. J Vasc Surg 1995; 22:524-31.
21. Shull KC, Nicolaides AN, Fernandes J, Miles C, Horner J, Needham T, Cooke ED, Eastcott FHG. Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. Arch Surg 1979; 114:1304-1306.
22. Nicolaides AN, Hussein MK, Szendro G, Christopoulos D, Vasdekis S, Clarke H. The relation of venous ulceration with ambulatory venous pressure measurements. J Vasc Surg 1993; 17:414-419.
23. Welkie JF, Comerota AJ, Katz ML, Aldridge SC, Kerr RP, White JV. Hemodynamic deterioration in chronic venous disease. J Vasc Surg 1992; 16:733-740.
24. Araki CT, Back TL, Padberg FT, Thompson PN, Jamil Z, Lee BC, Duran WN, Hobson RW II. The significance of calf muscle pump function in venous ulceration. J Vasc Surg 1994; 20:872-877.
25. Johnson BF, Manzo RA, Bergelin RO, Strandness DE. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one-to-six year follow-up. J Vasc Surg 1995;21:307-313.
26. Prandoni P, Frulla M, Sartor D, Concolato A, Girolami A. Venous abnormalities and the post-thrombotic syndrome. J Thromb Haemost 2005; 3:401-402.
27. Meissner MH, Manzo RA, Bergelin RO, Markel A, Strandness DE. Deep venous insufficiency: the relationship between lysis and subsequent reflux. J Vasc Surg 1993;18:596-608.
28. Meissner MH, Caps MT, Bergelin RO, Manzo RA, Strandness DE. Propagation, rethrombosis and new thrombus formation after acute deep venous thrombosis. J Vasc

Surg 1995; 22:558-567.

29. O'Shaughnessy AM, FitzGerald DE. The patterns and distribution of residual abnormalities between the individual proximal venous segments after an acute deep vein thrombosis. J Vasc Surg 2001; 33:379-384.
30. Kearon C, Kahn SR, Agnelli G, Goldhaber SZ, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: the American College of Chest Physicians' evidence-based clinical practice guidelines (8th edition). Chest Suppl 2008; 133(6):454S-545S.
31. Brandjes DPM, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349:759-762.
32. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. Am J Med 1984; 76:393-397.
33. Elliot MS, Immelman EJ, Jeffery P, Benatar SR, Funston MR, Smith JA, Shepstone BJ, Ferguson D, Jacobs P, Walker W, Louw JH. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. Br J Surg 1979; 66:838-843.
34. Arnesen H, Hoiseth A, Ly B. Streptokinase or heparin in the treatment of deep vein thrombosis. Acta Med Scand 1982; 211:65-68.
35. Goldhaber SZ, Vaughan DE, Markis JE, Selwyn AP, Meyerovitz MF, Loscalzo J, et al. Acute pulmonary embolism treated with tissue plasminogen activator. Lancet 1986; 2:886-888.
36. Goldhaber SZ, Meyerovitz MF, Markis JE, Kim D, Kessler CM, Sharma GVRK, et al. Thrombolytic therapy of acute pulmonary embolism: current status and future potential. J Am Coll Cardiol 1987; 10:96B-104B.
37. Goldhaber SZ, Kessler CM, Heit J, Markis J, Sharma GVRK, Dawley D, et al. Randomised controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. Lancet 1988; 2:293-298.
38. Goldhaber SZ, Kessler CM, Heit JA, Elliott CG, Friedenberg WR, Heiselman DE, Wilson DB, Parker JA, Bennett D, Feldstein ML, Selwyn AP, Kim D, Sharma GVRK, Nagel JS, Meyerovitz MF. Recombinant tissue-type plasminogen activator versus a novel dosing regimen of urokinase in acute pulmonary embolism: a randomized controlled multicenter trial. J Am Coll Cardiol 1992; 20:24-30.
39. Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507-511.
40. Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis: an international multicenter randomized trial. Chest 1994; 106:718-724.

41. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347(15):1143-1150.

42. Turpie AGG, Levine MN, Hirsh J, Ginsberg JS, Cruickshank M, Jay R, Gent M. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis: results of a randomized trial. Chest Suppl 1990; 97(4):172S-175S.

43. Goldhaber SZ, Meyerovitz MF, Green D, Vogelzang RL, Citrin P, Heit J, Sobel M, Wheeler HB, Plante D, Kim H, Hopkins A, Tufte M, Stump D, Braunwald E. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. Am J Med 1990;88:235-240.

44. Meyerovitz MF, Polak FJ, Goldhaber SZ. Short-term response to thrombolytic therapy in deep venous thrombosis: predictive value of venographic appearance. Radiology 1992;184:345-348.

45. Verstraete M, Miller GA, Bounameaux H, Charbonnier B, Colle JP, Lecorf G, Marbet GA, Mombaerts P, Olsson CG. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 1988; 77(2):353-360.

46. Mikkola KM, Patel SR, Parker A, Grodstein F, Goldhaber SZ. Increasing age is a major risk factor for hemorrhagic complications after pulmonary embolism thrombolysis. Am Heart J 1997; 134:69-72.

47. Kanter DS, Mikkola KM, Patel SR, Parker JA, Goldhaber SZ. Thrombolytic therapy for pulmonary embolism: frequency of intracranial hemorrhage and associated risk factors. Chest 1997; 111:1241-1245.

48. Vedantham S, Grassi CJ, Ferral H, Patel NH, Thorpe PE, Antonacci VP, Janne d'Othee BM, Hofmann LV, Cardella JF, Kundu S, Lewis CA, Schwartzberg MS, Min RJ, Sacks D for the Technology Assessment Committee of the Society of Interventional Radiology. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis. J Vasc Interv Radiol 2006; 17:417-434.

49. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology 1999; 211:39-49.

50. Laiho MK, Oinonen A, Sugano N, Harjola VP, Lehtola AL, Roth WD, Keto PE, Lepantalo M. Preservation of venous valve function after catheter-directed and systemic thrombolysis for deep venous thrombosis. Eur J Vasc Endovasc Surg 2004; 28:391-396.

51. Comerota AJ, Throm RC, Mathias SD, Haughton S, and Mewissen M. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. J Vasc Surg 2000; 32:130-137.

52. AbuRahma AF, Perkins SE, Wulu JT, Ng HK. Iliofemoral deep vein thrombosis: conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting.

Ann Surg 2001; 233(6):752-760.

53. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. Eur J Vasc Endovasc Surg 2002; 24:209-214.

54. Verhaeghe R, Stockx L, Lacroix H, Vermylen J, Baert AL. Catheter-directed lysis of iliofemoral vein thrombosis with use of rt-PA. Eur Radiol 1997; 7:996-1001.

55. Ouriel K, Gray B, Clair DG, Olin J. Complications associated with the use of urokinase and recombinant tissue plasminogen activator for catheter-directed peripheral arterial and venous thrombolysis. J Vasc Interv Radiol 2000; 11:295-298.

56. Shortell CK, Queiroz R, Johansson M, Waldman D, Illig KA, Ouriel K, Green RM. Safety and efficacy of limited-dose tissue plasminogen activator in acute vascular occlusion. J Vasc Surg 2001; 34:854-859.

57. Sugimoto K, Hofmann LV, Razavi MK, Kee ST, Sze DY, Dake MD, Semba CP. The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. J Vasc Surg 2003;37:512-517.

58. Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. J Vasc Interv Radiol 2004;15:347-352.

59. Kim HS, Preece SR, Black JH, Pham LD, Streiff MB. Safety of catheter-directed thrombolysis for deep venous thrombosis in cancer patients. J Vasc Surg 2008; 47:388-394.

60. Arapelly A, Hofmann LV, Kim HS, Geschwind JF, Kirkwood S, Oechsle D, Perler B. Weight-based rt-PA thrombolysis protocol for acute native arterial and bypass graft occlusions. J Vasc Interv Radiol 2002; 13:45-50.

61. Semba CP, Bakal CW, Calis KA, Grubbs GE, Hunter DW, Matalon TA, et al. Alteplase as an alternative to urokinase. Advisory Panel on Catheter-Directed Thrombolysis. J Vasc Interv Radiol 2000; 11:279-287

62. Semba CP, Murphy TP, Bakal CW, Calis KA, Matalon TS. Thrombolytic therapy with use of alteplase (rt-PA) in peripheral arterial occlusive disease: review of the clinical literature. J Vasc Interv Radiol 2000; 11:149-161.

63. Vedantham S, Thorpe PE, Cardella JF, Grassi CJ, Patel NH, Ferral H, Hofmann LV, Janne d'Othee BM, Antonacci VP, Brountzos EN, Brown DB, Martin LG, Matsumoto AH, Meranze SG, Miller DL, Millward SF, Min RJ, Neithamer CD, Rajan DK, Rholl KS, Schwartzberg MS, Swan TL, Towbin RB, Wiechmann BN, and Sacks D, for the CIRSE and SIR Standards of Practice Committees. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol 2006; 17:435-448.

64. Kasirajan K, McNamara TO, Vina RF, Ramaiah V, Diethrich EB, Fogarty TJ. Use of a mechanical thrombectomy infusion catheter with embolic protection for lower extremity deep venous thrombosis. J Vasc Interv Radiol Suppl 2003; 14 (2 Pt 2):S116.

65. Spencer E, Garby KB. Initial results with a new device, the Trellis, using isolated thrombolysis for treatment of lower extremity DVT. J Vasc Interv Radiol 2004; 15 (2 Pt 2):S152.

66. McNamara TO, Dong PR, Gomes A. New device/method for clearing iliofemoral venous thrombosis in the post operative period. J Vasc Interv Radiol Suppl 2004; 15(2 Pt 2):S153-S154.

67. Bush RL, Lin PH, Bates JT, Mureebe L, Zhou W, Lumsden AB. Pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis: safety and feasibility study. J Vasc Surg 2004; 40:965-970.

68. Lin PH, Zhou W, Dardik A, Mussa F, Kougias P, Hedayati N, et al. Catheter-direct thrombolysis versus pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis. Am J Surg 2006; 192(6):782-788.

69. Cynamon J, Stein EG, Dym RJ, Jagust MB, Binkert CA, Baum RA. A new method for aggressive management of deep vein thrombosis: retrospective study of the power pulse technique. J Vasc Interv Radiol 2006; 17:1043-1049.

70. Garcia M, Dignazio M, Kimbris G, Beeravolu A, Peters A, Veasey J. ATTACK-DVT: Angiojet and TPA thrombolysis – a closer look at combined therapy for the treatment of DVT. J Vasc Interv Radiol Suppl 2007; 18 (1 Pt 2):S21.

71. O'Sullivan GJ, Lohan DG, Gough N, Cronin CG, Kee ST. Pharmacomechanical thrombectomy of acute deep vein thrombosis with the Trellis-8 isolated thrombolysis catheter. J Vasc Interv Radiol 2007; 18(6):715-724.

72. Hilleman DE, Razavi MK. Clinical and economic evaluation of the Trellis-8 Infusion Catheter for deep vein thrombosis. J Vasc Interv Radiol 2008; 19:377-383.

73. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease. Chest 2004; 126:401S-428S.

74. Vedantham S, Millward SF, Cardella JF, Hofmann LV, Razavi MK, Grassi CJ, Sacks D, Kinney TB. Society of Interventional Radiology Position Statement: treatment of acute iliofemoral deep vein thrombosis with use of adjunctive catheter-directed intrathrombus thrombolysis. J Vasc Interv Radiol 2006; 17:613-616.

75. Vedantham S, Rundback JH, Comerota AJ, Hunter DW, Meissner MH, Hofmann LV, Horne M III, Gloviczki P, Andrews RT, Fan C, Hume KM, Goldhaber SZ, Tapson VF, Razavi MK, Min RJ. Development of a research agenda for endovascular treatment of venous thromboembolism: proceedings from a multidisciplinary consensus panel. J Vasc Interv Radiol 2005; 16:1567-1573.

76. Meissner MH, Eklof B, Gloviczki P, Lohr JM, Lurie F, Kistner R, Moneta G, Wakefield TW. Mapping the future: organizational, clinical, and research prioritites in venous disease. J Vasc Surg Suppl 2007; 46:84S-93S.

77. Kearon C, Julian JA, Newman TE, Ginsberg JS, for the McMaster Diagnostic Imaging Practice Guidelines Initiative. Non-invasive diagnosis of deep vein thrombosis. Ann Intern Med 1998; 128:663-677.

78. Lensing AW, Buller HR, Prandoni P, Batchelor D, Molenaar AH, Cogo A, Vigo M, Huisman PM, ten Cate JW. Contrast venography, the gold standard for the diagnosis of deep vein thrombosis: improvement in observer agreement. Thromb Haemost 1992; 67:8-12.

79. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130:461-470.

80. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. N Engl J Med 2006; 354:379-386.

81. Kahn SR, Shrier I, Ducruet T, Arsenault L, Miron M, Roussin A, et al. Prospective multicenter cohort study of the incidence, timing, and predictors of the post-thrombotic syndrome after symptomatic deep venous thrombosis. Abstract accepted for presentation at the International Society on Thrombosis and Haemostasis, Geneva, Switzerland on July10, 2007.

82. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. Ann Intern Med 2001; 135(2):112-123.

83. Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. Radiology 1994; 191:487-494.

84. Roy S, Laerum F, Brosstad F, Kvernebo K, Sakariassen KS. Sequestrated thrombolysis: comparative evaluation in vivo. Cardiovasc Interv Radiol 2000; 23:131-137.

85. Kasirajan K, McNamara TO, Demarais D, Koronkowski R, Leeflang S. Effect on hemolysis and residual thrombolytic drug activity with the Trellis Device. J Vasc Interv Radiol Suppl 2003; 14 (2 Pt 2):S112.

86. Ramaiah V, Del Santo PB, Rodriguez-Lopez JA, Gowda RG, Perkowski PE, Diethrich EB. Trellis thrombectomy system for the treatment of iliofemoral deep venous thrombosis. J Endovasc Ther 2003; 10:585-589.

87. Arko FR, Cipriano P, Lee E, Filis KA, Zarins CK, Fogarty TJ. Treatment of axillosubclavian vein thrombosis: a novel technique for rapid removal of clot using low-dose thrombolysis. J Endovasc Ther 2003; 10:733-738.

88. Semba CP, Weck S, Razavi MK, Setum CM, Patapoff T. Characterization of alteplase (tPA) following delivery through the AngioJet Rheolytic Catheter. J Endovasc Ther 2005;12:123-128.

89. Allie DE, Herbert CJ, Khan MH, et al. Novel simultaneous combination chemical thrombolysis/rheolytic thrombectomy therapy for acute critical limb ischemia: the power-pulse spray technique. Cath Cardiovasc Interv 2004; 63:512-522.

90. Ouriel K, Veith FJ, Sasahara A. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or

Peripheral Artery Surgery (TOPAS) Investigators. N Engl J Med 1998;338(16):1105-1111.

91. Tsai J, Georgiades CS, Hong K, Kim HS. Presumed pulmonary embolism following power-pulse spray thrombectomy of upper extremity venous thrombosis. Cardiovasc Interv Radiol 2006; 29:678-680.

92. Vedantham S, Vesely TM, Sicard GA, Brown D, Rubin B, Sanchez LA, Parti N, Picus D. Pharmacomechanical thrombolysis and early stent placement for iliofemoral deep vein thrombosis. J Vasc Interv Radiol 2004; 15:565-574.

93. Mickley V, Shwagierek R, Rilinger N, Gorich J, Sunder-Plassman L. Left iliac venous thrombosis caused by venous spur: treatment with thrombectomy and stent implantation. J Vasc Surg 1998; 28:492-497.

94. Kaufman JA, Kinney TB, Streiff MB, Sing RF, Proctor MC, Becker D, Cipolle M, Comerota AJ, Millward SF, Rogers FB, Sacks D, Venbrux AC. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology Multidisciplinary Consensus Conference. J Vasc Interv Radiol 2006; 17(3):449-460.

95. Millward SF, Grassi CJ, Kinney TB, Kundu S, Becker GJ, Cardella JF, Martin LG, Silberzweig JE, Sacks D, for the Technology Assessment Committee of the Society of Interventional Radiology. Reporting standards for inferior vena caval filter placement and patient follow-up: supplement for temporary and retrievable/optional filters. J Vasc Interv Radiol 2005; 16:441-443.

96. Kahn SR, Desmarais S, Ducruet T, Arsenault L, Ginsberg JS. Comparison of the Villalta and Ginsberg clinical scales to diagnose the post-thrombotic syndrome: correlation with patient-reported disease burden and venous valvular reflux. J Thromb Haemost 2006;4:907-908.

97. Milne AA, Stonebridge PA, Bradbury AW, Ruckley CV. Venous function and clinical outcome following deep vein thrombosis. Br J Surg 1994; 81:847-849.

98. Villalta S, Bagatella P, Piccioli A, Lensing AWA, Prins MH, Prandoni P. Assessment of reliability and reproducibility of a clinical scale for the post-thrombotic syndrome. Haemostasis 1994; 24:158a (abstract).

99. Porter JM, Moneta GL, and an International Consensus Committee on Chronic Venous Disease. Reporting standards in venous disease: an update. J Vasc Surg 1995; 21:635-645.

100. Beebe HG, Bergan JJ, Bergqvist D, Eklof B, Eriksson I, Goldman MP, et al. Classification and grading of chronic venous disease in the lower limbs: a consensus statement. Vasc Surg 1996; 30:5-11.

101. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004; 40:1248-1252.

102. Kahn SR, M'Lan CE, Lamping DL, Kurz X, Bérard A, Abenhaim L et al. The influence of venous thromboembolism on quality of life and severity of chronic venous disease. J

Thromb Haemost 2004; 2:2146-2151.

103. Kahn SR, M'lan CE, Lamping DL, Kurz X, Berard A, Abenhaim LA, for the VEINES Study Group. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. J Vasc Surg 2004;39:823-828.

104. Rutherford RB, Padberg FT, Comerota AJ, Kistner RL, Meissne MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000; 31:1307-1312.

105. Meissner MH, Natiello C, Nicholls SC. Performance characteristics of the venous clinical severity score. J Vasc Surg 2002; 36:889-895.

106. Kakkos SK, Rivera MA, Matsagas MI, Lazarides MK, Robless P, Belcaro G, Geroulakos G, et al. Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003; 38:224-228.

107. Ricci MA, Emmerich J, Callas PW, Rosendaal FR, Stanley AC, Naud S, Vossen C, Bovill EG. Evaluating chronic venous disease with a new venous severity scoring system. J Vasc Surg 2003; 38:909-915.

108. Ware JE, Snow KK, Kosinski MA, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center. 1993.

109. Kahn SR, Kearon C, Julian JA, MacKinnon B, Kovacs MJ, Wells P, Crowther MA, Anderson DR, Van Nguyen P, Demers C, Solymoss S, Kassis J, Geerts W, Rodger M, Hambleton J, Ginsberg JS for the ELATE Investigators. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. J Thromb Haemost 2005; 3:718-723.

110. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient- reported measure of symptoms and quality of life. J Vasc Surg 2003; 37:410-419.

111. Kahn SR, Ducruet T, Lamping DL, Arsenault L, Miron MJ, Roussin A, et al. The VEINES-QOL/Sym questionnaire is a valid and reliable measure of quality of life and symptoms in patients with deep vein thrombosis. J Clin Epidemiol 2006; 59(10):1049-1056.

112. Ware JE, Kosinski M, Keller S. SF-36 physical and mental summary measures: A user's manual. Boston: The Health Institute, New England Medical Center. 1994.

113. Streiner DL, Norman GR. Health measurement scales: A practical guide to their development and use (2nd. edition). Oxford: Oxford University Press; 1995.

114. Herr KA, Mobily PR, Kohout FJ, Wagenaar D. Evaluation of the Faces Pain Scale for use with the elderly. Clin J Pain 1998; 14(1):29-38.

115. Bernstein SL, Chang A, Esses D, Gallagher EJ. Relationship between intensity and relief in patients with acute, severe pain. Acad Emerg Med 2005; 12:158-159.

116. Marder VJ, Soulen RL, Atichartakarn V, Budzynski AZ, Parulekar S, Kim JR, Edward N, Zahavi J, Algazy KM. Quantitative venographic assessment of deep vein thrombosis in the

evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89(5):1018-1029.

117. Van Bemmelen PS, Bedford G, Beach K, Strandness DE. Quantitative segmental evaluation for venous valvular reflux with duplex ultrasound scanning. J Vasc Surg 1989;10:425-431.

118. Meissner MH, Caps T, Zierler B, Bergelin RO, Manzo RA, Strandness E. Deep venous thrombosis and superficial venous reflux .J Vasc Surg 2000; 32:48-56.

119. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3(4):692-694.

120. Sacks D, Marinelli DL, Martin LG, Spies JB, and the Members of the Society of Interventional Radiology Technology Assessment Committee. J Vasc Interv Radiol 2003;14 (9 Pt 2):S395-S404.

121. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells PS, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631-639.

122. Linkins LA, Stretton R, Probyn L, Kearon C. Interobserver agreement on ultrasound measurements of residual vein diameter, thrombus echogenicity, and Doppler venous flow in patients with previous venous thrombosis. Thromb Res 2006; 17:241-247.

123. Linkins L, Pasquale P, Paterson S, Kearon C. Change in thrombus length on venous ultrasound that supports a diagnosis of recurrent deep vein thrombosis. Arch Intern Med 2004; 164:1793-1796.

124. Prandoni P, Cogo A, Bernardi E, Villalta S, Polistena P, Simioni P, et al. A simple ultrasound approach for detection of recurrent proximal vein thrombosis. Circulation 1993;88:1730-1735.

125. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977; 296(13):716-721.

126. Gold MR, Patrick DL, Torrance GW, Fryback DG, Hadorn DC, Kamlet MS, et al. Identifying and valuing outcomes. New York, NY:Oxford University Press, 1996.

127. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002; 21(2):271-292.

128. Beck JR, Pauke SG. The Markov process in medical prognosis. Med Decis Making 1983;3(4):419-458.

129. Kahn SR, Ducruet T, Arsenault L, Miron MJ, Roussin A, Desmariais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Johri M, Shrier I, Lamping DL, Ginsberg J. Incidence, timing of onset and severity of post-thrombotic syndrome after acute symptomatic deep vein thrombosis: two-year results from a Canadian multicenter prospective cohort study (the VETO Study). Blood 2005; 106:1636 (abstract).

130. Kahn SR, Shbaklo H, Lamping DL, Holcroft CA, Shrier I, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Johri M, Ginsberg JS. Determinants of

health-related quality of life during the two years following deep venous thrombosis. J Thromb Haemost 2008; in press.

131. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. Ann Intern Med 2002; 136(3):254-259.

132. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002; 359(9302):248-252.

133. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. Lancet 2002; 359(9305):515-519.

134. Devereaux PJ, Manns BJ, Ghali WA, Quan H, Lacchetti C, Montori VM et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA 2001; 285(15):2000-2003.

135. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet 2002; 359(9306):614-618.

136. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357(9263):1191-1194.

137. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. Br Med J 2005; 330(7499):1049.

138. Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. Lancet 2005; 365(9465):1159-1162.

139. Ng CM, Rivera JO. Meta-analysis of streptokinase and heparin in deep vein thrombosis. Am J Health Syst Pharm 1998; 55(19):1995-2001.

140. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340:901-907.

141. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells PS, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631-639.

142. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 2002; 359(9308):781-785.

143. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. Br Med J 2002; 325(7365):652-654.

144. Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. Lancet 2005; 365(9471):1657-1661.

145. O'Donnell M, Kearon C, Julian J, Kahn SR, et al. Evaluation of a venous-return assist device (Venowave) to treat post-thrombotic syndrome: a randomized controlled trial http://www.controlled-trials.com/mrct/trial/VENOWAVE/1059/120351.html. The American

Journal of Cardiology 2006; 1:1-2.

146. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004; 141(10):781-788.

147. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees:helping them to do their job well. Lancet 2005; 365(9460):711-722.

148. Mueller PS, Montori VM, Bassler D, Koenig BA, Guyatt GH. Ethical issues in stopping randomized trials early because of apparent benefit. Ann Intern Med 2007;146(12):878-81.

149. Goodman SN. Stopping at nothing? Some dilemmas of data monitoring in clinical trials.Ann Intern Med 2007; 146(12):882-887.

150. Kuhle S, Koloshuk B, Marzinotto V, Bauman M, Massicotte P, Andrew M, et al. A cross-sectional study evaluating post-thrombotic syndrome in children. Thromb Res 2003;111:227-233.

151. Bjarnason H, Kruse JR, Asinger DA, Nazarian GK, Dietz CA, Caldwell MD, et al. Iliofemoral deep venous thrombosis: safety and efficacy outcome during 5 years of catheter-directed thrombolytic therapy. J Vasc Interv Radiol 1997; 405-418.

152. Rodger MA, Kahn SR, LeGal G, Solymoss S, Chagnon I, Anderson DR, Wells PS, Kovacs MJ. Inter-observer reliability of measures to assess the post-thrombotic syndrome. Thromb Haemost 2008; in press.

153. Villalta S, Prandoni P, Cogo A, Bagatella P, Piccioli A, Bernardi E, et al. The utility of non-invasive tests for detection of previous proximal-vein thrombosis. Thromb Haemost 1995;73:592-596.

154. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 1997; 82:423-428.

155. Kahn SR, Azoulay L, Hirsch A, Haber M, Strulovitch C, Shrier I. Effect of graduated compression stockings on leg symptoms and signs during exercise in patients with deep venous thrombosis: a randomized cross-over trial. J Thromb Haemost 2003; 1:494-499.

156. Frulla M, Marchiori A, Sartor D, Mosena L, Tormene D, Concolato A, et al. Elastic stockings, hydroxyethylrutosides, or both for the treatment of post-thrombotic syndrome. Thromb Haemost 2005; 93:183-185.

157. Kolbach DN, Neumann HAM, Prins MH. Definition of the post-thrombotic syndrome, differences between existing classifications. Eur J Vasc Endovasc Surg 2005; 30:404-414.

158. Partsch H. Immediate ambulation and leg compression in the treatment of deep vein thrombosis. Dis Mon 2005; 51:135-140.

159. Prandoni P, Villalta S, Polistena P, Bernardi E, Cogo A, Girolami A. Symptomatic deep-vein thrombosis and the post-thrombotic syndrome. Haematologica 1995; 80:42-48.

160. Bullano MF, Willey V, Hausch O, Wygant G, Spyropoulos AC, Hoffman L. Longitudinal

evaluation of health plan cost per venous thromboembolism or bleed event in patients with a prior venous thromboembolism event during hospitalization. J Manag Care Pharm 2005;11(8):663-673.

161. Knight KK, Wong J, Hausch O, Wygant G, Aguilar D, Ofman JJ. Economic and utilization outcomes associated with choice of treatment for venous thromboembolism in hospitalized patients. Value Health 2005; 8(3):191-200.

162. Lapidus L, Borretzen J, Fahlen M, Thomsen HG, Hasselblom S, Larson L, et al. Home treatment of deep vein thrombosis. An outpatient treatment model with once-daily injection of low-molecular-weight-heparin (tinzaparin) in 555 patients. Pathophys Haemost Thromb 2002;32(2):59-66.

163. Lee M, Pao D, Hsu T, Sonderskov A. Cost savings and effectiveness of outpatient treatment with low molecular weight heparin of deep vein thrombosis in a community hospital. Can J Clin Pharm 2004; 11(1):e17-e27.

164. O'Brien JA, Caro JJ. Direct medical cost of managing deep vein thrombosis according to the occurrence of complications. Pharmacoeconomics 2002; 20(9):603-615.

165. Rodger MA, Gagne-Rodger C, Howley HE, Carrier M, Coyle D, Wells PS. The outpatient treatment of deep vein thrombosis delivers cost savings to patients and their families, compared to inpatient therapy. Thromb Res 2003; 112(1-2):13-18.

166. Kim HS, Patra A, Paxton BE, Khan J, Streiff MB. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. J Vasc Interv Radiol 2006; 17(7)1099-1104.

167. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York, NY: Oxford University Press, 1996.

168. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. JAMA 1996; 276(14):1172-1177.

169. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. JAMA 1996; 276(16):1339-1341.

170. Task Force on Principles for Economic Analysis of Health Care Technology. Ann Intern Med 1995; 122:61-70.

171. Luce BR, Manning WG, Siegel JE, Lipscomb J. Estimating costs in cost-effectiveness analysis. New York, NY: Oxford University Press, 1996.

172. Finkler SA. The distinction between cost and charges. Ann Intern Med 1982; 96(1):102-109.

173. Kahn SR, Ducruet T, Johri M, Arsenault L, Miron MJ, Roussin A, et al. The economic burden of deep venous thrombosis during the first 4 months following diagnosis: a prospective evaluation. Blood 2003; a710.

174. Hlatky MA, Rogers WJ, Johnstone I, Boothroyd D, Brooks MM, Pitt B, et al. Medical care costs and quality of life after randomization to coronary angioplasty or coronary bypass surgery. Bypass Revascularization Investigation (BARI) Investigators. N Engl J Med

1997;336(2):92-99.

175. Weintraub WS, Mauldin PD, Becker E, Kosinski AS, King SB III. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). Circulation 1995; 92(10):2831-2840.

176. Mark DB, Nelson CL, Anstrom KJ, Al Khatib SM, Tsiatis AA, Cowper PA, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation 2006;114(2):135-142.

177. Taira DA, Seto TB, Siegrist R, Cosgrove R, Berezin R, Cohen DJ. Comparison of analytic approaches for the economic evaluation of new technologies alongside multicenter clinical trials. Am Heart J 2003; 145(3):452-458.

178. Drug Topics Red Book. New York, NY: Hearst Business Publications, 1998.

179. Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, et al. Stroke after thrombolysis. Mortality and functional outcomes in GUSTO-1 trial. Global Use of Strategies to Open Occluded Coronary Arteries. Circulation 1995; 92(10):2811-2818.

180. Oldridge N, Furlong W, Feeny D, Torrance G, Guyatt G, Crowe J, et al. Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction. Am J Cardiol 1993; (72)2):154-161.

181. Gold MR, Patrick DL, Torrance GW, Fryback DG, Hardorn DC, Kamlet MS, et al. Identifying and valuing outcomes. New York, NY: Oxford University Press, 1996.

182. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Medical Care 2004; 42(9):851-859.

183. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Medical Care 1996; 34(7):702-722.

184. Fryback DG, Lawrence WF, Martin PA, Klein R, Klein BE. Predicting quality of well-being scores from the SF-36: results from the Beaver Dam Health Outcomes Study. Med Decis Making 1997; 17(1):1-9.

185. Johannesson M, Isacson DGL, Borgquist L. The relationship between health-state utilities and the SF-12 in a general population. Med Decis Making 1999; 19:128-140.

186. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Statistics in Medicine 2000; 19(23):32:3219-3236.

187. Efron B. An introduction to the bootstrap. New York, NY: Chapman & Hall, 1993.

188. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997; 6(4):327-340.

189. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983;

3(4):419-458.

190. Cohen DJ, Breall JA, Ho KK, Weintraub RM, Kuntz RE, Weinstein MC, et al. Economics of elective coronary revascularization. Comparison of costs and charges for conventional angioplasty, directional atherectomy, stenting and bypass surgery. J Am Coll Cardiol 1993;22(4):1052-1059.

191. Kuntz KM, Tsevat J, Goldman L, Weinstein MC. Cost-effectiveness of routine coronary angiography after acute myocardial infarction. Circulation 1996; 94(5):957-965.

192. Kuntz KM, Kent KC. Is carotid endarterectomy cost-effective? An analysis of asymptomatic patients. Circulation 1996; 94(9 Suppl 2):194 –198.

193. Wordsworth S, Ludbrook A. Comparing costing results in across country evaluations: the use of technology specific purchasing power parities. Health Econ 2005; 14(1):93-99.

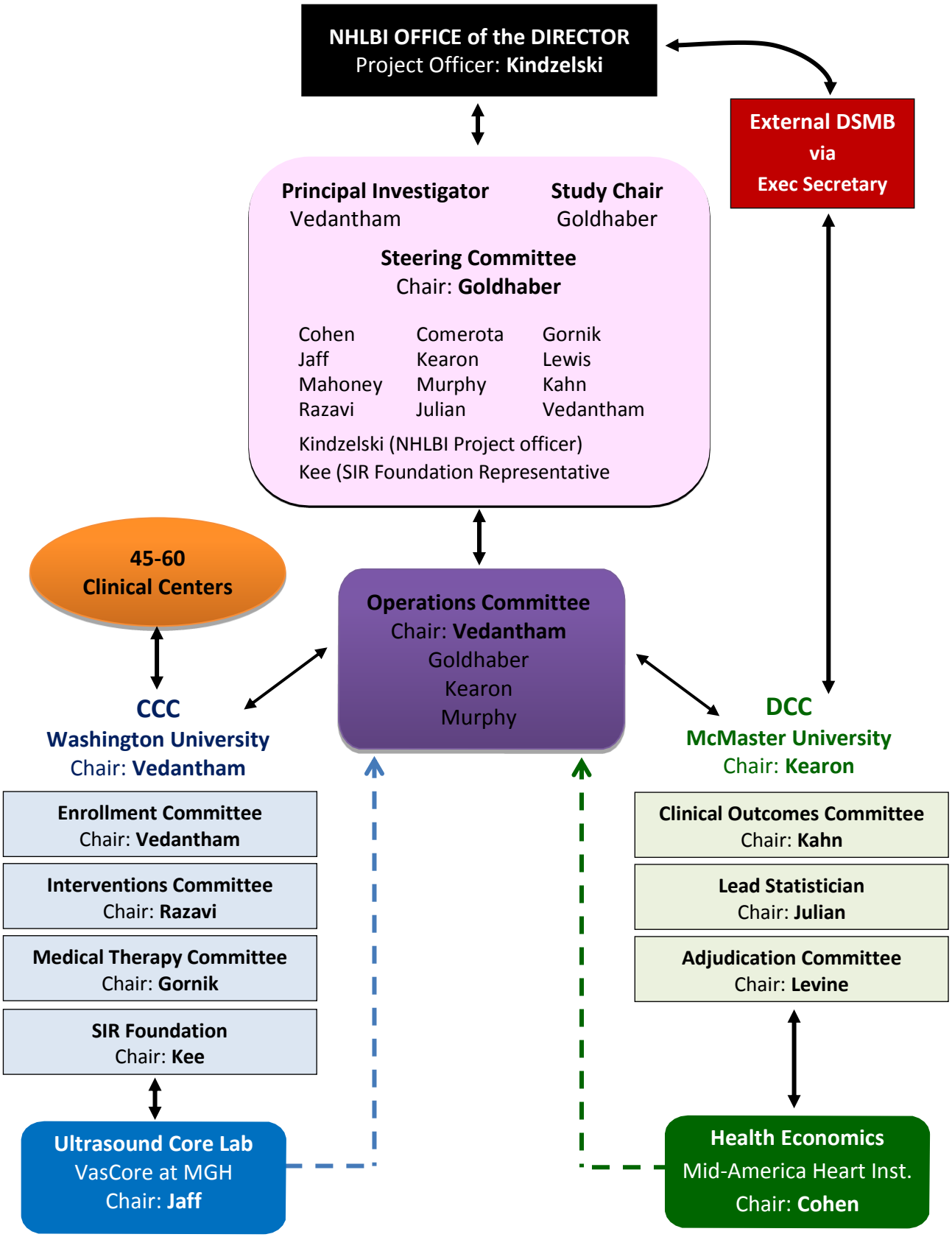
194. Hunink MG, Bult JR, de Vries J, Weinstein MC. Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. Med Decis Making 1998; 18(3):337-346.

195. Manning WG, Fryback DG, Weinstein MC. Reflecting uncertainty in cost-effectiveness analysis. New York, NY: Oxford University Press, 1996.

196. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. Medical Care 1994; 32(2):150-163.

197. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998; 18 (2 Suppl):S68-S80.

Appendix 1: ATTRACT Trial Organization



ATTRACT Trial: LEADERSHIP and COMMUNICATIONS

National Heart Lung and Blood Institute:

Andrei Kindzelski, M.D., Ph.D. (NHLBI Project Officer)

Steering Committee:

Samuel Z. Goldhaber, M.D. (Chair)
David Cohen, M.D.
Anthony Comerota, M.D.
Heather Gornik, M.D.
Michael Jaff, D.O.
Jim Julian, M.Math.
Susan Kahn, M.D.
Clive Kearon, M.D., Ph.D (Chair, Data Coordinating Center)
Stephen Kee, M.D. (SIR Foundation Representative)
Andrei Kindzelski, M.D. (NHLBI Project Officer)
Lawrence Lewis, M.D.
Elizabeth Magnuson, Ph.D.
Timothy Murphy, M.D.
Mahmood Razavi, M.D.
Suresh Vedantham, M.D. (Principal Investigator)

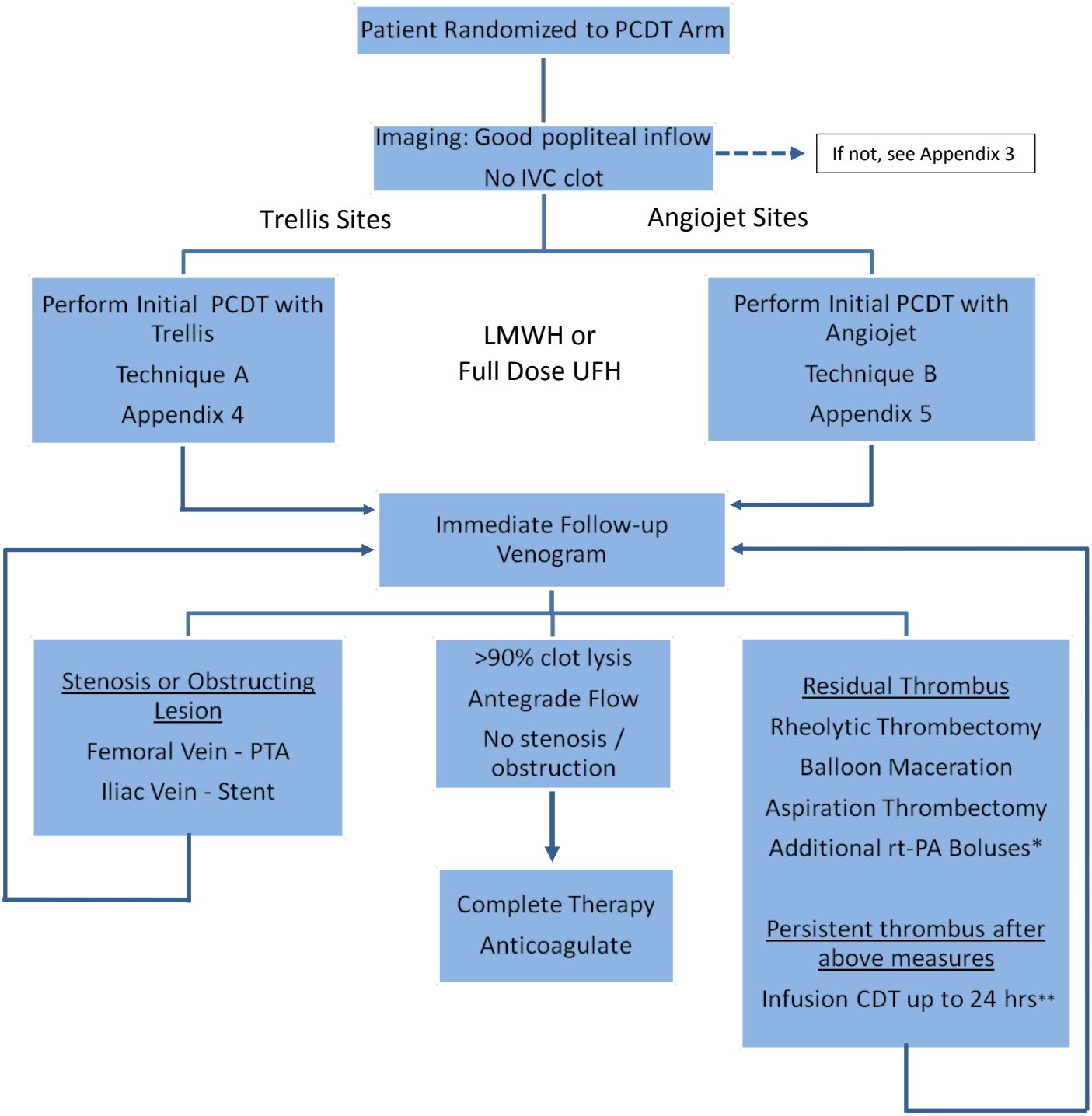
Operations Committee:

Suresh Vedantham, M.D. (Chair)
Samuel Z. Goldhaber, M.D.
Clive Kearon, M.D., Ph.D.
Timothy Murphy, M.D.

Administration and Coordination of the ATTRACT Trial:

To ensure seamless coordination between the study leadership, CCC, DCC, Core Laboratories, and Clinical Centers, the following communications structure will be employed: a) the Steering Committee will meet annually and will teleconference every 3 months; b) the Operations Committee will coordinate the day-to-day study operations and will teleconference weekly; c) the chairs of the Core Laboratories and committees will report to the chairs of the CCC and DCC monthly; d) the chairs of the 3 groups responsible for the major data domains (Dr. Kahn – Clinical Outcomes; Dr. Cohen – Health Economic; Dr. Jaff – Ultrasound), and other committee chairs as needed, will join Operations Committee calls periodically; e) study leadership will meet with Clinical Center personnel at the yearly Investigator Meetings and at routine site monitoring visits; and f) Dr. Vedantham will regularly speak with the Clinical Center investigators.

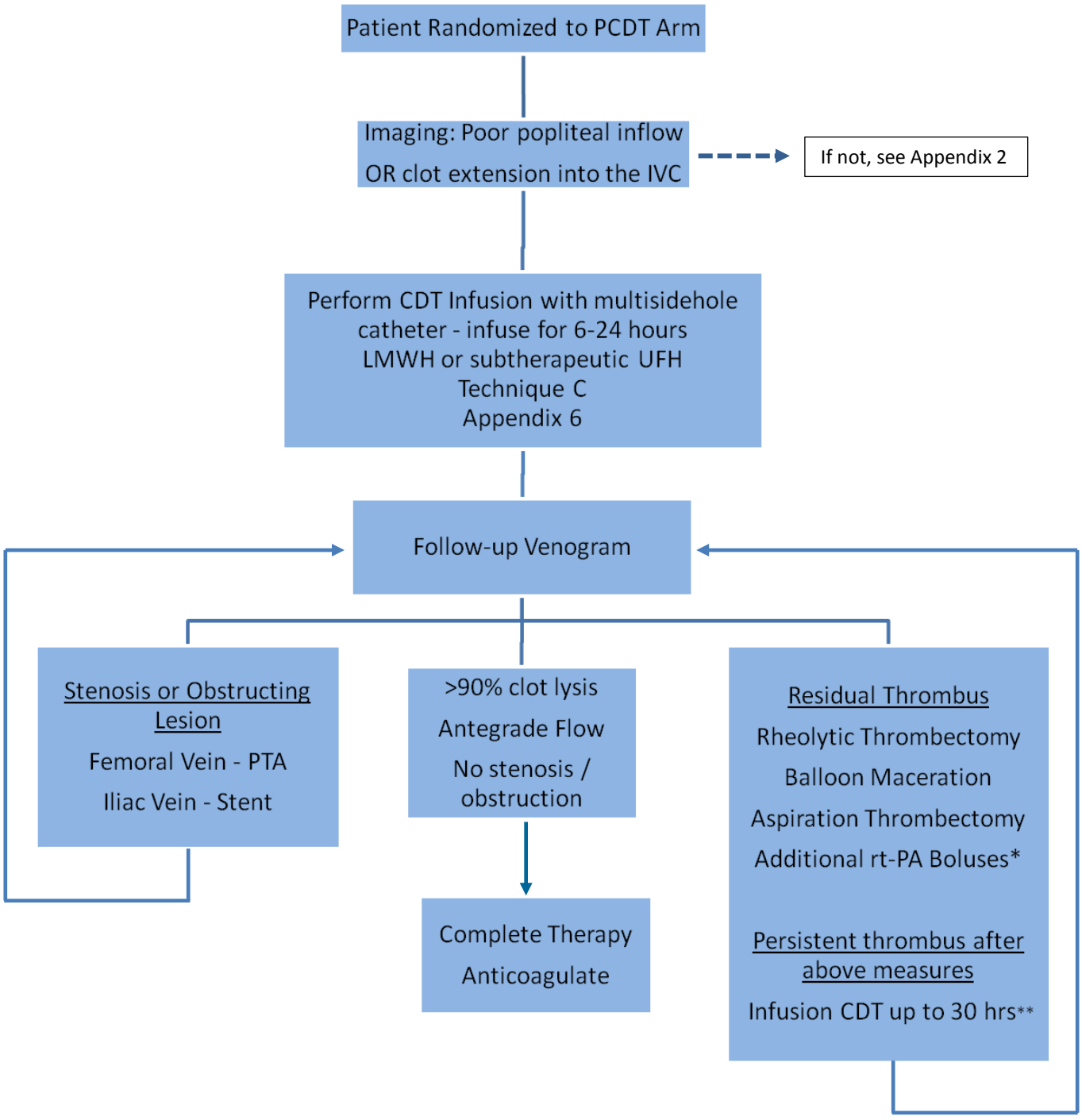
Appendix 2: Flow Chart – Single-Session PCDT



* The rt-PA may be delivered via a standard catheter, the sheath, the Trellis (Technique A patients only), or the Angiojet (Technique B patients only). The total dose for the initial procedure session may not exceed 25mg. The total rt-PA infusion time (not counting periods when the rt-PA infusion is turned off) cannot exceed 24 hours.

** The total rt-PA dose for all treatment sessions together may not exceed 35mg.

Appendix 3: Flow Chart – Infusion-First PCDT



* The rt-PA may be delivered via a standard catheter or the vascular sheath.

** The total rt-PA dose for all sessions together may not exceed 35mg. The total rt-PA infusion time for the entire treatment (not counting periods when the continuous rt-PA infusion is turned off) may not exceed 30 hours.

Appendix 4: Protocol for Trellis PCDT (Technique A)

1. Review the initial venogram and estimate the length of the clotted venous segment. For patients with ≤ 12cm thrombus, select a Trellis-8 Catheter with a 15cm treatment zone. For patients with > 12cm thrombus, select a Trellis-8 Catheter with a 30cm treatment zone.
2. Obtain an rt-PA solution from the pharmacy: 25mg rt-PA in 25ml Sterile Water (1 mg/ml).
3. Calculate the initial rt-PA dose to be delivered into the thrombus according to the following formula: **1mg per 3-4cm thrombus length (which equals 0.25 - 0.33mg rt-PA per cm thrombus length), with a minimum dose of 4mg**. For patients with thrombus exceeding 24cm, two runs of the Trellis-8 Catheter are needed to optimally distribute and disperse the rt-PA within the entire thrombosed venous segment – the initial rt-PA dose should be divided proportionally to evenly distribute the drug within the thrombus. For example, for a patient with 36cm of venous thrombus, if the physician chooses to use rt-PA at 1mg per 3cm thrombus length, the total dose would be 12mg. This could be divided evenly between the cephalad (6mg) and caudal (6mg) segments.
4. Prepare the rt-PA solution needed for the first run of the Trellis-8 Catheter as follows: Place the rt-PA intended for the first run of the Trellis-8 Catheter into a 10ml syringe, and dilute to a total volume of 10ml in normal saline. For the 15cm Trellis-8 Catheter, which is only used when the thrombus length is 12cm or less, this will result in 4mg rt-PA per run. For the 30cm Trellis-8 Catheter, this will typically result in 3-8mg per run (corresponding to 12 - 24cm thrombus length). As the total volume to be injected for each run will always be 10ml, the concentration of the injected rt-PA solution will therefore range from 0.3 - 0.8 mg/ml rt-PA.
5. Advance the Trellis-8 Catheter over the guidewire and position its cephalad balloon just above the highest extent of the thrombus. Inflate the cephalad and caudal balloons with dilute contrast, taking care not to over-inflate past the radiopaque markers on the Catheter.
6. Perform a stepped infusion of rt-PA into the thrombus. First inject 2ml of rt-PA solution into the infusion port of the Trellis-8 Catheter – this will instill 1ml of the rt-PA solution into the thrombus, with an additional 1ml filling the Catheter lumen. Activate the Dispersion Wire of the Trellis-8 for 10 minutes. During oscillation, inject 1ml of the rt-PA solution every minute (after 9 minutes, inject 1ml normal saline to clear the Catheter of rt-PA). Every minute, move the translation bar on the Oscillation Drive Unit to disperse the rt-PA within the clot.

7. After 10 minutes have passed, reduce the speed of the Dispersion Wire to one-third of full speed. De-activate and remove the Dispersion Wire and allow the rt-PA to dwell for an additional 5 minutes. Deflate the caudal balloon. At the physician's discretion, the rt-PA remaining within the isolated treatment zone may be aspirated via a syringe applied to the aspiration port of the Trellis-8 Catheter. Deflate the cephalad balloon. If the initial thrombus extent was less than or equal to 24cm, remove the Trellis-8 Catheter over a guidewire.
8. If the initial thrombus extent exceeded 24cm, re-position the Trellis-8 caudally to include the remaining thrombus and repeat Steps 4-7 above using the rt-PA planned for the second run. Remove the Trellis-8 Catheter over a guidewire and repeat the venogram.
9. If residual thrombus is present, an additional 10-minute run (with 5-minute dwell) of the Trellis-8 may be performed in <u>each</u> of the 1-2 treated segments using the method in Steps 4-8 above (additional rt-PA dose chosen by physician but the rt-PA must be dissolved in 10 ml solution and **the physician may not exceed the 25mg rt-PA dose limit for the initial PCDT session**). Note: for any single session, the Trellis activation time may not exceed 30 minutes in a single treatment area or 60 minutes overall for multiple treatment areas.
10. If needed, consult the Trellis Peripheral Infusion System Instructions for Use (package insert) for additional clarification on the appropriate use of the Trellis system.
11. See **Section 7.3.1** for details on concomitant heparin use during use of Technique A.
12. Return to **Section 7.3.5**. Please note that Technique A patients may receive no more than 24 hours of rt-PA infusion after the initial PCDT session.

Appendix 5: Protocol for AngioJet PCDT (Technique B)

1. Review the initial venogram and estimate the length of the clotted venous segment. Prepare an AngioJet DVX or Solent Proxi Catheter as prompted by the Angiojet Drive Unit.
2. Obtain an rt-PA solution from the pharmacy: 25mg rt-PA in 25 ml Sterile Water (1 mg/ml).
3. Calculate the initial rt-PA dose to be delivered into the thrombus according to the following formula: **1mg per 3 - 4cm thrombus length (which equals 0.25 - 0.33mg rt-PA per cm thrombus length), with a minimum dose of 4mg**. Assuming that the thrombus length varies between 3 - 60cm among different patients, this will result in rt-PA doses of 4 - 20mg. For example, for a 36cm venous segment, if the physician chooses to use 1mg per 3cm thrombus length, the dose would be 12mg.
4. Deliver rt-PA into the thrombus using either the PowerPulse or Rapid Lysis methods:
5. PowerPulse method: Prepare the rt-PA solution as follows: Dilute the planned rt-PA dose to a total volume of 50 - 100ml (determined by the physician) in normal saline (this will result in a rt-PA concentration ranging from 0.04 - 0.40 mg/ml). Put the AngioJet Drive Unit into PowerPulse mode. Advance the AngioJet Catheter over the guidewire and position it just above the cephalad aspect of the thrombus. Pulse-spray the rt-PA into the thrombus by depressing the foot pedal during slow withdrawal and advancement of the AngioJet Catheter through the thrombus (1cm every 3 seconds) over the wire. Allow the rt-PA to dwell within the thrombus for 30 minutes. Proceed to Step 5.
6. Rapid Lysis method: Prepare the rt-PA solution as follows: Dilute the planned rt-PA dose to a total volume of 250-500ml (determined by the physician) in normal saline (this will result in a rt-PA concentration ranging from 0.008 - 0.080 mg/ml). Advance a standard hockey-stick shaped guide catheter over the guidewire and position it just above the cephalad extent of the thrombus. Put the AngioJet Drive Unit into Aspiration mode. Advance the AngioJet Catheter through the guide catheter and position the tip of the AngioJet Catheter just beyond the tip of the guide catheter. Using the rt-PA solution as the infusate, activate the AngioJet Catheter during slow withdrawal and advancement of the AngioJet Catheter and guide catheter (they may be moved as a single unit) through the thrombus (about 1cm every 3 seconds) over the wire. Proceed to Step 5.
7. With the AngioJet Drive Unit in Aspiration Mode, activate the AngioJet to aspirate

thrombus by depressing the foot pedal during slow withdrawal and advancement of the AngioJet Catheter through the thrombus over the guidewire. To increase access of the AngioJet Catheter to thrombi located peripherally within the vein, the use of a standard hockey-stick shaped guiding catheter to orient the device during aspiration is encouraged. Perform two back-and-forth passes of the AngioJet Catheter through the thrombus, then remove it.

8. Caution: During the procedure, if using a DVX Catheter, do not retract the guidewire into the DVX Catheter. If retraction of the guidewire into the DVX Catheter occurs, remove the DVX Catheter and guidewire from the patient and back-load the DVX Catheter over the guidewire. This will prevent the wire tip from exiting and binding in the Catheter windows. Also, when using the AngioJet in the iliac vein and/or IVC, physicians are encouraged to include rest periods of at least 10 seconds after every 30 seconds of device activation time.
9. **The total rt-PA dose for the initial session may not exceed 25mg.** The AngioJet activation time and infusate volume should not exceed 8 minutes and 500ml, respectively.
10. If needed, consult the Instructions for Use (package insert) for the AngioJet System, DVX Catheter, and/or Solent Proxi Catheter for additional clarification on their appropriate use.
11. See **Section 7.3.1** for details of concomitant heparin use during use of Technique B.
12. Return to **Section 7.3.5**. Please note that Technique B patients may receive no more than 24 hours of rt-PA infusion after the initial PCDT session.

Appendix 6: Protocol for Infusion-First PCDT (Technique C)

1. Review the initial venogram and estimate the length of the clotted venous segment. Advance a multisidehole catheter into position with its sideholes spanning the thrombus.
2. Obtain the following rt-PA solution from the pharmacy: 10mg rt-PA in 10 ml Sterile Water for Injection, USP, diluted to a total volume of 1000 ml in 0.9% normal saline (rt-PA concentration 0.01 mg/ml). Infuse through the multisidehole catheter at a rate of 50-100 ml/hr (corresponding to 0.01 mg/kg/hr, with maximum allowable dose 1.0 mg/hr). For patients in whom fluid volume is of concern or in whom an ultrasound infusion catheter is selected, the physician may concentrate the rt-PA solution to 0.02 mg/ml - 0.04 mg/ml (10mg rt-PA in 250-500 ml total volume, infused at 12.5 - 50 ml/hr). If more than one venous access site is used, the rt-PA dose may be split per physician discretion. The physician may also utilize the vascular sheath (with or without added sideholes) to infuse part of the rt-PA. All infusion catheters should be used per their Instructions for Use (package insert).
3. During infusion CDT, the patient should be placed at bedrest and the affected leg should be elevated. Mechanical compression adjuncts may be used per the physician's standard practice. If UFH is used, it should be infused at subtherapeutic levels (6-12 units/kg/hr, maximum allowable dose 1000 units/hr) through the vascular sheath (preferably) or through a peripheral IV (if the sheath is being used to infuse rt-PA), to a target PTT of less than 2 times control. The patient should be monitored in an ICU or stepdown unit and peripheral blood taken at least every 12 hours for hemoglobin, partial thromboplastin time (PTT), and platelet count. A fibrinogen level may be obtained if this is the physician's standard practice.
4. The rt-PA infusion may be halted temporarily or permanently at physician discretion if there is evidence of bleeding (see Section 7.3.4), the PTT > 100 seconds, or the fibrinogen level < 100 mg/dl. When rt-PA is stopped, saline should be infused to maintain catheter patency.
5. After 6-24 hours, the patient should return to the procedure suite. At each return visit, follow the procedures described in **Section 7.3.5**. In particular, the use of rheolytic thrombectomy is encouraged at the first follow-up visit to speed thrombolysis (see **Appendix 5**, Steps 5-9).
6. Technique C patients may receive no more than 30 hours of rt-PA infusion.

Appendix 7: Justification for Using the Villalta PTS Scale

Evidence of the Reliability of the Villalta PTS Scale

A. In Villalta's study (98), 100 patients were evaluated 6-36 months after venogram-proven DVT. A physician asked the patient to rate the degree to which his/her leg condition interfered with daily life as none, mild, moderate, or severe. Two other physicians independently evaluated the patient, scored the presence of PTS symptoms and signs, and summed the results into a total "Villalta score". Receiver-operator curve (ROC) analysis was used to select optimal cutoff values for the presence and severity (mild, moderate, severe) of PTS, where the criterion standard was interference with the patient's daily life by the condition. Inter- observer agreement was found to be high by the weighted kappa test for PTS signs (0.77), symptoms (0.80), total score (0.78), and PTS severity category (0.75). Interference with the patient's daily life (i.e. clinically important PTS disease burden) was best predicted by the total Villalta score. The sensitivity and specificity of the chosen threshold Villalta score values in discriminating patients with PTS from those without PTS, and between different severity categories, were high.
B. In a 50-patient substudy to VETO (multicenter DVT cohort study), inter-observer (physician-nurse) reliability coefficients for all clinical sign scale components were moderate to high (weighted kappas 0.59 - 0.84) and the total Villalta score showed even stronger correlations (Pearson coefficient 0.88, $p < 0.0001$) (81).
C. In a 125-patient substudy to REVERSE (multicenter VTE cohort study), the total Villalta score showed excellent inter-observer reliability (Pearson coefficient 0.86 – 0.91) that exceeded that of the composite clinical sign score (0.70 - 0.75) and the individual clinical sign scores (152).

Hence, all 3 studies found the Villalta Scale to have excellent inter-observer reliability.

Evidence of the Acceptability of the Villalta PTS Scale to DVT Patients and Physicians

The Villalta PTS Scale has been used to identify cases of incident PTS in proximal DVT patients in cross- sectional (10,153) and cohort studies (1,2,5,12,81,129,154), single-center trials (3,4,155,156), and multicenter trials (109). It is the only PTS measure to be successfully used in a multicenter randomized DVT treatment trial (109). Evidence that the Villalta Scale is considered to be a valid method of measuring PTS by physicians is found in the American College of Chest Physicians' 2008 guidelines' strong recommendation in favor of use of elastic compression stockings in DVT patients, which is based upon proof of PTS prevention in studies using the Villalta PTS Scale (3,4,30).

Evidence of the Validity of the Villalta PTS Scale: Correlation with Health Impairment (QOL)

The construct validity of Villalta's PTS Scale is supported by the demonstration that the total Villalta scores have significantly correlated with QOL in three independent study populations:

A. In a small (n=41) study (10) of outpatients with first-episode proximal DVT, the presence of PTS on Villalta's PTS Scale, PTS severity category by total Villalta score, and the total Villalta score as a continuous variable ($r = -0.63$) all correlated strongly with poorer venous disease-specific QOL ($p < 0.001$).
B. In 145 patients enrolled in the ELATE Trial (a multicenter trial comparing two intensities of warfarin for proximal DVT), the presence of PTS on Villalta's PTS Scale correlated strongly with poorer venous disease-specific QOL (6.9 points on VEINES-QOL, $p < 0.0001$) and physical generic QOL (7.4 points on SF-36 Physical Component score, $p = 0.0002$) (109).
C. In 359 DVT patients in the VETO Study, the presence of PTS on Villalta's PTS scale independently predicted worsened disease-specific QOL ($p < 0.001$) and, to a lesser degree, generic QOL ($p = 0.04$) (12). Evidence of discriminant validity is seen in the fact that the total Villalta score did not correlate with sex, a variable not expected to relate to PTS. In addition, the presence of PTS on Villalta's Scale was shown to be a better predictor of clinically important PTS than imaging criteria such as the presence of valvular reflux on Duplex ultrasound (96). Overall, the strong, graded correlations between the total Villalta scores and venous disease-specific QOL in populations of DVT patients indicate that Villalta's PTS Scale measures a physical condition of major health importance that is closely related to clinically important chronic venous disease (i.e. clinically important PTS).

Evidence of the Validity of the Villalta PTS Scale: Correlations with Venous Disease Indicators

Further evidence that Villalta's PTS Scale is a valid measure of PTS is derived from its **associations with known anatomic/physiologic findings of venous disease**: 1) Abnormal Venograms: In 100 patients with lower extremity symptoms who had undergone venography for suspected DVT > 3 months earlier, Villalta's PTS Scale successfully distinguished patients who did have DVT (positive venograms) from those who did not (negative venograms) (153); 2) Venous Ultrasound Abnormalities: In proximal DVT patients, the presence of PTS on Villalta's PTS Scale was associated with a higher likelihood of Duplex ultrasound venous abnormalities at 6 months ($p < 0.001$) (26); 3) Elevated Ambulatory Venous Pressures (AVP): In 124 DVT patients, mean AVP increased in graded fashion with increasing PTS severity category on

Villalta's PTS Scale (29 mmHg for no PTS, 41 mmHg for mild/moderate PTS, 66 mmHg for severe PTS, $p < .001$) (157).

Evidence of the <u>Responsiveness</u> of the Villalta PTS Scale to Clinical Change

Patients who reported improvement in generic and venous disease-specific QOL over 4 month-period after a DVT episode showed significant reductions in Villalta score during that time ($p < 0.001$)(12). Hence, based upon the overall weight of evidence, the Villalta PTS Scale is an excellent method to establish the presence of clinically important PTS (1-6,12,26,81,96,98,109, 111,129,152-159).

Appendix 8: Villalta Questionnaire

Assessment of Symptoms of PTS (Villalta)

Patient ID: XXX **Date of assessment:** dd/mmm/yyyy

SYMPTOMS (complete for both legs):

Please ask the patient to complete the questions on this page. The nurse or physician performing the assessment of clinical signs of PTS must be blind to these responses.

Q.1 In general, how would you rate the following SYMPTOMS in your **RIGHT** leg? (***please check one response for each symptom***)

	No or Minimal	**Mild**	**Moderate**	**Severe**	
Cramps	☐	☐	☐	☐	
Itching	☐	☐	☐	☐	
Pins and needles	☐	☐	☐	☐	**RIGHT LEG**
Leg heaviness	☐	☐	☐	☐	
Pain	☐	☐	☐	☐	

Q.2 In general, how would you rate the following SYMPTOMS in your **LEFT** leg? (***please check one response for each symptom***)

	No or Minimal	**Mild**	**Moderate**	**Severe**	
Cramps	☐	☐	☐	☐	
Itching	☐	☐	☐	☐	
Pins and needles	☐	☐	☐	☐	**LEFT LEG**
Leg heaviness	☐	☐	☐	☐	
Pain	☐	☐	☐	☐	

Appendix 8: Villalta Questionnaire (cont'd)

Assessment of Clinical Signs of PTS (Villalta)

Patient ID: XXXX **Date of Assessment**: dd/mmm/yyyy **Time of Assessment:** hh:mm *AM* ☐ *PM* ☐

SIGNS (complete for both legs):

This form is to be completed by the nurse or physician performing assessment of PTS. Nurse or physician must be blind to responses to previous Symptoms questions.

Q.1 Rate the following SIGNS on the **RIGHT** leg ***(please check one response for each sign)***

	No or Minimal	Mild	Moderate	Severe	
Pretibial edema	☐	☐	☐	☐	
Skin induration	☐	☐	☐	☐	
Hyperpigmentation	☐	☐	☐	☐	**RIGHT LEG**
Venous ectasia	☐	☐	☐	☐	
Redness	☐	☐	☐	☐	
Pain during calf compression	☐	☐	☐	☐	

Is an ulcer present? No ☐ Yes ☐

Circumference 10 cm below tibial tuberosity _ _ cm

Q.2 Rate the following SIGNS on the **LEFT** leg ***(please check one response for each sign)***

	No or Minimal	Mild	Moderate	Severe	
Pretibial edema	☐	☐	☐	☐	
Skin induration	☐	☐	☐	☐	
Hyperpigmentation	☐	☐	☐	☐	**LEFT LEG**
Venous ectasia	☐	☐	☐	☐	
Redness	☐	☐	☐	☐	
Pain during calf compression	☐	☐	☐	☐	

Is an ulcer present? No ☐ Yes ☐

Circumference 10 cm below tibial tuberosity _ _ cm

Appendix 9: Revised CEAP Classification of Chronic Venous Disease

C Clinical signs (grade 0-6) supplemented by A for asymptomatic and S for symptomatic presentation

E Etiologic classification (Congenital, Primary, Secondary)

A Anatomic distribution (Superficial, Deep, or Perforator, alone or in combination)

P Pathophysiologic dysfunction (Reflux or Obstruction, alone or in combination)

C (Clinical) Classification

Class 0	No visible or palpable signs of venous disease
Class 1	Telangiectasies or reticular veins
Class 2	Varicose veins
Class 3	Edema
Class 4a	Skin changes including pigmentation or venous eczema
Class 4b	Skin changes including lipodermatosclerosis
Class 5	Healed venous ulceration
Class 6	Active venous ulceration

E (Etiological) Classification

Ec (Congenital)	The etiology of the chronic venous disease has been present since birth
E_P (Primary)	Idiopathic chronic venous disease
Es (Secondary)	Chronic venous disease with known etiology (e.g. post-thrombotic)
En	No venous cause identified

A (Anatomical) Classification

Superficial veins (A_S)
Deep veins (A_D)
Perforating veins (A_P)
No venous location identified (An)

P (Pathophysiological) Classification

Reflux (P_R)
Obstruction (P_O)
Both (P_{RO})
No venous pathophysiology seen (P_N)

Example:

A patient with healed ulcerations known to be related to post-thrombotic syndrome, with documented reflux and obstruction, would be classified as $\mathbf{C}_5\mathbf{E}_S\mathbf{A}_D\mathbf{P}_{RO}$.

Appendix 10: Venous Clinical Severity Score

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain or other discomfort (i.e. aching, heaviness, fatigue, soreness, burning)	None	Occasional pain or discomfort (i.e. not restricting regular daily activity)	Daily pain or discomfort (i.e. interfering with but not preventing regular daily activities)	Daily pain or discomfort (limits most regular daily activities)
Varicose veins Must be ≥ 3 mm to qualify	None	Few, scattered: (i.e. isolated branch VVs or clusters), includes corona phlebectatica	Multiple: confined to calf or thigh	Multiple: involves calf and thigh
Venous edema Presumes venous origin (i.e. not brawny, not pitting or spongy edema and relieved by elevation)	None	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee or above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e. vasculitis purpura)	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (i.e. erythema, cellulites, eczema, dermatitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (i.e. chronic edema with fibrosis, hypodermitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Number of active ulcers	0	1	2	≥ 3
Active ulcers: duration (longest active)	None	< 3 months	> 3 mo, < 1 year	Not healed for >1 year
Active ulcers: size (largest active)	N/A	< 2 cm diameter	2-6 cm diameter	> 6 cm diameter

Appendix 11: Quality of Life Questionnaire

SF-36 and VEINES

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

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

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c Lifting or carrying groceries	☐1	☐2	☐3
d Climbing several flights of stairs	☐1	☐2	☐3
e Climbing one flight of stairs	☐1	☐2	☐3
f Bending, kneeling, or stooping	☐1	☐2	☐3
g Walking more than a mile	☐1	☐2	☐3
h Walking several hundred yards	☐1	☐2	☐3
i Walking one hundred yards	☐1	☐2	☐3
j Bathing or dressing yourself	☐1	☐2	☐3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

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

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

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

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

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

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
I Did you feel tired?	☐1	☐2	☐3	☐4	☐5

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

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

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

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d My health is excellent	☐1	☐2	☐3	☐4	☐5

You have had a venous thrombosis. We are interested in finding out more about the effects of your leg problem on your daily activities, both at home and at work.

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

(Check one box on each line)

	Every day	Several times a week	About once a week	Less than once a week	**Never**
a Heavy legs	☐1	☐2	☐3	☐4	☐5
b Aching legs	☐1	☐2	☐3	☐4	☐5
c Swelling	☐1	☐2	☐3	☐4	☐5
d Night cramps	☐1	☐2	☐3	☐4	☐5
e Heat or burning sensation	☐1	☐2	☐3	☐4	☐5
f Restless legs	☐1	☐2	☐3	☐4	☐5
g Throbbing	☐1	☐2	☐3	☐4	☐5
h Itching	☐1	☐2	☐3	☐4	☐5
i Tingling sensation (e.g. pins and needles)	☐1	☐2	☐3	☐4	☐5

13. At what time of day is your leg problem most intense?
(Check one)

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 12: Venous Duplex Scan Procedure

Baseline Ultrasound Exams (692 subjects):

This protocol is strongly recommended to evaluate the proximal lower extremity deep veins for DVT, and to characterize its extent. The exam should ideally include the iliac veins from iliocaval confluence through the popliteal vein to the tibial vein confluence.

Iliac Veins – Compression and Color Doppler: Examination of the iliac veins should be conducted in a warm room after an 8-hour fast to minimize overlying bowel gas. The patient should be supine with the head slightly elevated to minimize muscular rigidity. The transducer frequency should be selected based upon the depth of the vessel. The transducer should be placed at the level of the umbilicus to identify the iliocaval confluence in a transverse view. The sonographer should follow the course of the common iliac vein of interest, in gray scale. The common and external iliac veins should be examined for vessel wall motion, compressibility (if possible on some patients and in some segments, like the external iliac vein), and the absence or presence of intraluminal echoes. After completing the gray scale evaluation of the iliac veins, the spectral Doppler and color Doppler evaluation should commence, from a longitudinal view. The Doppler evaluation of the iliac veins is critical to determine patency since compressibility is limited. The common and external iliac veins should be examined and the waveforms documented. Waveforms should be assessed for spontaneity and respiratory phasicity. Color Doppler should be optimized to visualize flow patterns within the iliac veins. Color should not be seen outside the vessel walls as this may overwrite intraluminal echoes from thrombus. Color Doppler images should be recorded to display iliac vein filling.

Lower Extremity Veins - Compression: Next, the veins within the lower extremity should be examined from common femoral vein through the popliteal vein. The transducer frequency should be selected based upon the depth of the vessel. The patient should be placed in a semi-fowlers position to assist in filling of the deep veins. The patient should be instructed to shift weight to the ipsilateral hip to aid external rotation of the limb with the knee slightly flexed. Attention should be paid to ensuring patient comfort to minimize muscular rigidity during external compression with the probe. The probe should be placed just below the inguinal ligament and a transverse view of the common femoral vein (CFV) above the saphenofemoral junction should be obtained. External pressure from the transducer should be applied to coapt/collapse the vessel walls. Release of compression should also be carefully observed to confirm that the examiner did not roll off the vein during compression. The sonographer should continue compressions moving inferiorly at 1 - 2cm increments to the saphenofemoral junction, femoral

vein and into the popliteal vein. The entire course of each segment should be compressed. If probe pressure does not completely collapse the vein, increased pressure should be used – if the accompanying artery begins to deform then adequate pressure is confirmed. Any area that does not compress must be evaluated from both sagittal and transverse views to determine the reason for lack of compression. Images of the vein segments should be documented prior to and during compression. If a vein segment does not compress, the gray scale image should be enhanced to identify the absence or presence of low level echoes. If echoes are present where the vein is not compressible, the location and extent of the thrombus, the vessel size, and the absence or presence of flow should be documented.

Lower Extremity Veins – Pulsed & Color Doppler: From a longitudinal view, the Doppler sample volume should be placed within the lumen of the CFV. Flow patterns should be assessed from common femoral, femoral, and popliteal veins for spontaneity, respiratory phasicity and augmentation. Augmentation may be documented using color Doppler.

Characteristics of a normal venous Doppler signal are:

1. *Spontaneous:* Blood flow present without augmentation maneuvers
2. *Respiratory phasicity:* Blood flow velocity changes with respiration or valsalva
3. *Augmentation:* Blood flow velocity increases with distal limb compression or with release of proximal limb compression.

Interpretation of Baseline Ultrasound Exams: Exam interpretation will be based on the following criteria: 1) compression unequivocally excludes the presence of thrombus; 2) when compression is limited, such as in the iliac veins, the diagnosis is weighted more heavily on the Doppler waveform findings, symmetry of both common femoral vein waveforms, and the presence of color flow (although the absence of color flow by itself does not necessarily indicate DVT), but must be confirmed by venogram or CT scan for purposes of evaluating study eligibility.

A test is negative when:

1. The vein compresses (vessel walls coapt) when extrinsic pressure is applied;
2. The lumen of the vein is echo-free; and
3. The venous Spectral Doppler waveforms and color Doppler document normal flow patterns and normal color filling

Criteria for diagnosing acute DVT:

- Non-compressible or incompletely compressible common femoral vein or femoral vein at the site of thrombus or intraluminal echoes

- Presence of intraluminal echoes, abnormal Doppler waveform, and absence of color filling in the iliac vein are suggestive of DVT (for purposes of evaluating eligibility, confirmation with venogram or contrast-enhanced CT scan is needed)
- Also suggestive: echoes display the following characteristics: echoes disfigure during compression; only seen with acute DVT and regular shape and edges.
- 4mm increase in compressed thrombus diameter at site of DVT, or ≥ 10cm increase in thrombus margin compared with prior study

1-Year Follow-Up Ultrasound Exams (142 subjects in 7 selected Clinical Centers):

Venous valve closure time is assessed to determine the absence or presence of venous valvular reflux. Valve closure time (VCT) is measured from the spectral Doppler waveform obtained at designated sites in the deep venous system. The exam should be performed with the patient standing in a warm room, with weight placed on the non-study limb with the knee of the study limb flexed slightly. Restrictive clothing, belts, shoes, stockings, girdles, etc. should be removed. Imaging should be performed using a 5 to 7.5MHz linear array transducer (lower frequency transducer may be necessary if the veins are deeper than 5cm). Additional equipment should include automated cuff inflator/deflator with a 24cm cuff for the common femoral vein and a 12cm cuff for the popliteal vein. The 24cm cuff should be wrapped around the thigh leaving sufficient room to place the transducer. The 12cm cuff should then be placed just below the knee.

The transducer should first be placed in the groin to obtain a sagittal view of the common femoral vein and saphenofemoral junction. The spectral Doppler and color Doppler settings should be optimized. The Doppler sample volume should be placed just below the level of the saphenofemoral junction. While insonating the vein, the thigh cuff should be rapidly inflated to 80 mmHg - when flow has ceased for approximately 3 seconds, the cuff should be rapidly deflated (over less than 0.3 seconds). The Doppler waveforms should be recorded to evaluate for reflux. Significant reflux can also be captured by color flow Doppler, and if this is evident it should be documented by obtaining images of the flow reversal. A minimum of two readings should be obtained minimize technical errors.

For evaluation of reflux at the level of the popliteal vein, the patient should be asked to turn around (back facing technologist). The transducer should be placed in the popliteal fossa, and a sagittal view of the popliteal vein should be obtained. The Doppler sample volume should be placed in the popliteal vein below the saphenopopliteal junction. If the saphenopopliteal junction is not visualized, the sample volume should be placed in the mid-popliteal vein. The 12 cm cuff

should be rapidly inflated to 100 mmHg while recording the Doppler spectral waveforms. When flow has ceased for approximately 3 seconds, the cuff should be rapidly deflated (over less than 0.3 seconds). Reflux should be documented by recording the spectral Doppler waveforms. A minimum of 2 readings should be obtained.

Criteria for Reflux: reversed flow component ≥ 0.5 seconds.

Appendix 13: Health Economic Study

BACKGROUND AND RATIONALE

As previously noted, there are over 200,000 first episodes of DVT diagnosed each year in the U.S., with subsequent development of PTS in 25-50% (1-5). PTS is associated with a tremendous burden to patients in terms of physical limitations and poor quality of life, and to society in terms of the high cost of treatment and lost productivity due to disability (7-12). Consequently, the identification of cost-effective approaches for the treatment of DVT is critical. Previous studies have examined costs associated with the initial treatment of and long-term complications following DVT. An analysis of data from administrative claims databases for 2 large U.S. healthcare plans from 1998-2000 reported average costs for incident DVT events not involving pulmonary embolism (PE) of $7,712 ± $18,339 (median, $3131), and costs for DVT events involving PE of $12,200 ± $24,038 (median $6678). Over a 21 month follow-up period, one in 4 of these patients experienced an average of 1.24 bleed or recurrent VTE events that required hospitalization, with associated average costs of $14,957 per event (160). A model-based study of the economic burden of long-term DVT complications following Hip Replacement Surgery in the U.S., based on published estimates of the incidence and prognosis of PTS and recurrent VTE, found that the annual per-patient costs of mild-to-moderate PTS was $839 in the first year and $341 in subsequent years, annual costs of severe PTS were $3817 in the first year and $1677 in subsequent years, and the annual long-term cost of diagnosis and treatment of recurrent DVT and PE events were estimated at $3798 and $6404, respectively (14).

As the management of DVT has evolved from hospitalization for intravenous heparin therapy to outpatient treatment with LMWH and use of interventional strategies including stand-alone CDT and PCDT, some studies have documented the variable economic impact of different management strategies. A study of hospitalized patients with DVT based on 1999-2000 administrative data from 132 U.S. hospitals found that treatment with LMWH was associated with significantly lower total hospitalization costs than treatment with UFH, although UFH was used in 67% of admissions (161). Higher total medication costs for LMWH treated patients ($736 vs. $539) were more than offset by lower overall hospitalization costs (total hospitalization costs: $3018 for LMWH versus $3732 for UFH), largely explained by shorter mean length of stay (4.4 days vs. 5.8 days). Several additional recent studies have documented that for patients with uncomplicated DVT, self-administered LMWH in a homecare setting is associated with significantly lower costs and no observed difference in outcome (162-165).

Three recent studies comparing costs and outcomes following stand-alone CDT and PCDT

reported similar clinical outcomes but significantly lower hospitalization costs for PCDT due to lower thrombolytic doses and infusion times and decreased length of stay (68,72,166).

By randomizing 692 patients to PCDT + optimal standard DVT therapy versus optimal standard DVT therapy alone, ATTRACT offers an ideal opportunity to estimate the cost-effectiveness of PCDT for the treatment of acute DVT. The estimation of cost-effectiveness is particularly important given the high up-front costs associated with the PCDT procedure and the large number of patients. The relative benefit of PCDT with respect to the prevention of PTS, and the extent to which the higher upfront costs of the PCDT procedure are offset by downstream cost savings associated with avoidance of PTS will be central factors underlying the results of the cost-effectiveness study, and its implications for future patient care and health policy.

Cost-effectiveness analysis is a formal technique for relating costs and medical effectiveness in order to maximize the overall health benefits available to society (or to any policy-making unit), subject to the constraint of fixed resources. By explicitly quantifying the tradeoffs between health care costs and health benefits, cost-effectiveness analysis allows physicians to compare the health benefits gained by use of a new treatment to those benefits that could be achieved by alternative uses for the same health care resources. The cost-effectiveness ratio is the formal representation of this tradeoff and is calculated as the net change in health care costs (measured in dollars) associated with the new treatment divided by the net change in medical effectiveness (measured in years of life gained or quality-adjusted years of life gained) (167-170).

METHODS

1. Overview of the ATTRACT Health Economic Study

The goals of the ATTRACT health economic study are to compare 2-year economic outcomes in patients with symptomatic acute proximal DVT randomized to either PCDT + optimal standard DVT therapy versus optimal standard DVT therapy alone, and if PCDT is found to be both efficacious and associated with increased costs, to carry out a formal cost-effectiveness analysis to estimate the incremental cost per quality-adjusted life year gained with PCDT.

2. Data Collection Overview

The general approach to data collection will be to integrate collection of the economic data as much as possible into the mainstream activities of each ATTRACT Clinical Center. For example, the medical resource utilization data required for this study will be collected on the standard clinical Case Report Forms. Follow-up medical encounters, resource utilization, and measures

of indirect costs will also be collected on Case Report Forms using a standardized, structured interview at patient follow-up times. Utility measurements will be obtained from the quality of life assessment by means of self-administered questionnaires given to each patient at the time of the study enrollment and follow-up. Once these data have been entered and cleaned by the DCC, they will be transmitted in electronic format to the Health Economic Core Laboratory.

On the other hand, collection of certain data elements requires additional training and will be performed directly by trained personnel from the Health Economic Core Laboratory. For example, collection of itemized hospital bills and UB92 summary bills will be performed directly by the Core Laboratory. These tasks will be performed centrally since they involve retrospective data collection, which is easily accomplished in batched format and requires specialized data abstraction skills that are beyond those required of most clinical research coordinators.

3. Patient Population

All patients who participate in the ATTRACT trial will be eligible for the Health Economic Study.

4. Economic Data

Cost data will be collected for each study patient from the point of study intake until the completion of the planned 2-year follow-up period. To facilitate analysis from a variety of potential perspectives, overall costs will be calculated for three categories: direct medical costs, custodial and chronic care costs, and indirect costs. Direct medical costs will include the cost of any inpatient care, outpatient care (including outpatient procedures, diagnostic testing, and prescription medications), and emergency room visits. Custodial and chronic care costs will include the cost of nursing home care, rehabilitation services (inpatient or outpatient), visiting nurses, home health aides, and other non-physician health professionals. Indirect medical costs will include the cost of care provided by other family members, such as lost wages. As recommended by the National Panel on Cost-Effectiveness in Health and Medicine, costs of lost work or other earnings on the part of the patient will be tabulated separately, but not included in the calculation of medical care costs for the primary cost-effectiveness analysis (171).

A. Data Collection: The following specific data will be collected for each randomized patient:

1. Costs of the index PCDT procedure: operating room or angiographic suite costs, including lab time, anesthesia time, recovery room time, equipment costs (guidewires, thrombectomy devices, embolus protection devices, guiding catheters, sheaths, and other devices used), rt-PA use, adjunctive medication use (including anticoagulants), and the amount and type of

radiographic contrast required. These data will provide a direct measure of resource utilization for the PCDT procedures and thus allow accurate determination of the cost of these procedures using standard, resource-based accounting methods (172).

2. Measures of global resource utilization for the initial hospitalization and all follow-up hospitalizations, including length of stay, number of ICU days, principal diagnosis (ICD-9 codes), major procedures, complications, and DRG assignment. As described below, hospital admissions unrelated to treatment of venous disease or its complications (including PE and bleeding) will be identified at trial completion by a clinical events committee that is blinded to treatment assignment, and excluded from the economic analysis.
3. Itemized hospital charges and summary bills (UB-92 forms) for the index hospitalization and follow-up hospitalizations for treatment of venous disease or its complications (see below).
4. Detailed outpatient medications including type of medication and daily dose for all medications used for the prevention and treatment of venous disease or its complications, including over the counter medications.
5. Purchase and use of prescription compression stockings, bandages and other devices, during each follow-up interval.
6. Self-reported estimates of medical resource utilization including the number of emergency room visits and physician visits during follow-up. In addition, we will obtain patient (or proxy) self-report estimates of the number of visits by allied health professionals including visiting nurses, home health aides, occupational therapists, and physical therapists during follow-up.
7. Number and duration of admissions to rehabilitation hospitals, nursing homes, and other chronic care facilities.

Hospitalization-related resource utilization data will be collected at each protocol-mandated clinic visit by the local research coordinator using standardized Case Report Forms and source-verified based on review of pertinent medical records. Utilization of other medical services including outpatient care, prescription medications, custodial care, and rehabilitation services as well as loss of work by the patient and any other caregivers will be assessed by detailed questionnaires that will be administered by the local research coordinators at the time of each scheduled clinical follow-up. The accurate reporting of health care resource use data will be aided by the weekly recording by the patient of medical care resource use in a cost diary, which the patient will be instructed to bring to each follow-up visit. This form will also record resource use related to indirect costs, including transportation to and from non-protocol mandated hospital

and doctor's visits, and lost time from work and decreased work productivity. Previous experience with such a diary by Dr. Kahn (ATTRACT Steering Committee member) and co-investigators in the Venous Thrombosis Outcomes cohort (VETO) study has demonstrated a high level of patient acceptability, and the ability to use it to derive useful and valid DVT-specific resource utilization (173). Before study initiation, personnel from the Health Economic Core Laboratory will train the Clinical Center personnel in appropriate completion of the data forms.

B. Hospital Billing Data:

In addition to detailed health care resource utilization data, we will collect comprehensive hospital billing information (itemized hospital charges and UB-92 summary bills) for each study participant for the index hospitalization and for any subsequent hospital admissions during the follow-up period. Together with cost-to-charge conversion factors, these hospital bills will be used to derive cost estimates for inpatient medical care services that are directly applicable to the study population. Hospital billing information will be collected by an experienced research assistant at the Health Economic Core Laboratory, working in conjunction with the local research coordinators and the Director of Patient Accounts at each participating Clinical Center. To assist in collection of billing data, the Health Economic Core Laboratory will generate a monthly summary of hospital admissions that will be forwarded directly to the Clinical Center's billing department. Prior to enrollment, patients will be asked provide permission to obtain such billing records, and all related data will be kept in a secure, confidential database.

5. Estimation of Costs

In the U.S. healthcare system, it is possible to collect medical billing information that provides detailed and objective summary measures of total medical resource consumption during hospital-based care. Because of the distortions present in hospital charges, however, it is necessary to convert raw billing data to an estimate of true medical care costs (172). A standard approach has been developed to do this and is described in detail below. Medical billing data have been successfully used as the primary measure of hospital cost in several major randomized trials of cardiovascular therapies (174-176).

An alternative to the use of hospital billing data is the use of Medicare DRG reimbursement rates. Although this has the advantage of representing the true "cost" of hospital services to a single large payer (Medicare), they have the strong disadvantage of being insensitive to shifts in resource use that do not affect DRG assignment, a particularly important limitation for the treatments under investigation in ATTRACT, and the reason that we will not use this approach.

A. Method of Hospital Cost Calculation: Hospitalization costs will be assessed by a combination

of resource-based costs and hospital billing data (177). Index Procedures - From the detailed resource use and procedure duration data recorded for the index procedure, costs will be calculated as the product of resource use and unit cost for each component. Acquisition costs for each item will be estimated as the average over several study hospitals.

B. Post-procedure Hospital Care: Costs for all other aspects of care during the initial hospitalization will be estimated based on hospital billing data. After excluding charges associated with the index procedure (for patients randomized to PCDT), post-procedure hospital costs will be determined by multiplying the remaining hospital charges by the hospital and cost-center specific cost-to-charge ratio obtained from the hospital's Medicare cost report (177). For patients for whom billing data are unavailable (expected to be < 10%), post-procedural hospital costs will be estimated based on a regression model developed from hospital admissions for which billing information is available, using multiple imputation. Multiple imputation techniques will be used rather than a single cost coefficient for each resource to preserve patient-to-patient variability within the study population. Costs will be converted to U.S. dollars corresponding to the last year of the trial, using the medical care component of the Consumer Price Index.

For any rehospitalizations for which standardized hospital billing information cannot be obtained (expected to be < 5% of total hospital admissions) or are non-existent (i.e., admissions to VA hospitals, non-U.S. hospitals, or other U.S. hospitals that do not generate UB-92 summary bills), inpatient medical care costs will be estimated based on a regression model derived from the hospitalizations for which bills are available, using multiple imputation, as will be done for the estimation of post- index procedure hospital costs, described above. Candidate resources for the imputation model would include length of stay, ICU length of stay, in-hospital events and complications, and major tests and procedures performed during the admission.

C. Elimination of Hospitalization Costs Unrelated to Venous Disease: Hospital admissions unrelated to treatment of venous disease or its complications will be excluded from our economic analysis, since any differences in these events are unlikely to be related to the treatment strategy. Thus, their inclusion would only increase the variance of our cost estimates. A clinical events committee blinded to treatment assignment will review each hospital admission during the study to determine whether it should be excluded from the economic analysis.

D. Estimation of Other Costs: Costs for professional services (i.e. physician fees for inpatient care, procedures, outpatient visits, and testing) will be based on measured resource utilization (taken from the medical record and patient self-reports) and national average reimbursements (from Medicare Fee Schedule). Outpatient care costs will be assigned using the Medicare Fee

Schedule. Drug costs will be based on wholesale prices in the Drug Topics Red Book (178).

Costs of home health care, long-term care, and custodial care will be based on average Medicare reimbursements for the services provided. Costs of additional home health and custodial services not covered by Medicare will be based on average charges, estimated from sources such as the U.S. Nursing Home Survey (171). The cost of care provided by family members will be estimated as the cost of lost employment required to provide this care. These costs will be estimated based on average national wages among persons in the work force.

All costs will be valued in year 2010 dollars, which is anticipated to be the final year for which national average cost data are expected to be available at the completion of the study. Costs measured during years other than 2010 will be converted to constant dollars using the appropriate component of the Consumer Price Index. Costs will not be discounted for the primary cost comparisons, but will be discounted at a rate of 3% per year for the cost-effectiveness analyses (see below) as recommended by the U.S. Public Health Service Guidelines on Cost-Effectiveness in Medicine (167).

6. Utility Measurement

For the purposes of cost-effectiveness analysis, quality of life must be measured in terms of "utility", a global rating (on a 0-1 scale) that reflects an individual's preference for his or her current health state relative to perfect health (125). Although in the past, it had been customary to measure utility directly from the trial participants using time-tradeoff techniques (179,180) there is an emerging consensus that cost-effectiveness analyses designed to inform societal resource allocation use **community-based** (rather than patient-based) preferences (181).

There are several potential techniques for measurement of patient-specific, population-based utility weights within ATTRACT. These include the Health Utilities Index (HUI), the Quality of Well-Being Scale (QWB), the EuroQol (EQ-5D), and recently published algorithms that allow mapping of the SF-36 or SF-12 to health state utilities (127,182-185). For ATTRACT, our preferred approach will be to calculate preference-based utility scores from the SF-36 data being collected in the QOL study, using a recently-validated scoring algorithm developed by Brazier et al (182). This has the advantage of using population-based utility weights that are appropriate to the analytic perspective of the analysis (i.e., U.S. societal weights). Although we are unaware of previous studies using the SF-36 as a utility measure for this population, the fact that the SF-36 has been previously shown to be a valid and responsive measure of health status for patients with PTS suggests that it will be appropriate for the ATTRACT population (10,12). As the SF-36 is already being used as the generic health status measure in the trial, this will also help to limit

the burden to both the patients and the study coordinators.

ANALYTIC PLAN AND STATISTICAL METHODS

1. Cost Analysis

The primary cost analysis will compare mean cumulative 2-year medical care costs between the two treatment groups. Secondary cost comparisons will be performed in an analogous fashion at alternative time points, including 1-month after randomization and 1-year after randomization. Decisions regarding the efficient allocation of resources generally involve consideration of the total costs of treating all patients with a specific disease with the treatment in question. In such settings, the arithmetic mean, which is the per-person cost of implementing the treatment, is the most relevant measure for summarizing and comparing cost (186). Measures of mean cost are the most appropriate reflection of the expected value of resource consumption to society — the appropriate metric for rational resource allocation. Characteristics of cost distributions can complicate the task of the data analyst needing to carry out a formal comparison of mean costs. In particular, the distribution of cost data tends to be skewed, with a large proportion of costs at the lower end of the distribution and a long right tail. As the appropriateness of many statistical tests and models relies on an approximately normal underlying distribution of the data, many common tests, such as the two-sample t test for comparison of means, may not be appropriate. An alternative method for comparing the average cost of two alternative treatments is through application of the non-parametric bootstrap approach to statistical inference (187). The bootstrap approach has been advocated as the most appropriate general method for comparing arithmetic mean costs as it can be used to draw inferences about the difference in mean costs between treatment groups without making any distributional assumptions (188). Confidence intervals around all cost estimates and differences in costs between treatment groups for the ATTRACT Trial will be derived using the bootstrap approach. Few patients should be lost to clinical follow-up during the study. For patients who are lost to follow-up, medical care costs beyond the time of last contact will be imputed using multiple imputation techniques, where the model includes the previous years' cost for the individual. This approach is reasonable as previous studies have found that the best predictor of subsequent healthcare resource utilization for a given patient is that patient's previous pattern of utilization.

2. Cost-Effectiveness Analysis

A formal cost-effectiveness analysis will be relevant if the clinical trial reveals a significant benefit of PCDT in terms of the primary study endpoint and if that benefit comes at additional cost. This analysis will use the societal perspective as recommended by the National Panel on

Cost-Effectiveness in Health and Medicine (167) and will be based, to the extent possible, on the empirical data from the trial. Cost effectiveness will be calculated as:

$$\frac{\text{Lifetime Cost (PCDT)} - \text{Lifetime Cost (optimal standard therapy)}}{\text{Effectiveness (PCDT)} - \text{Effectiveness (optimal standard therapy)}}$$

where effectiveness is measured in terms of quality-adjusted life years (QALYs).

A. Derivation of In-trial Quality-adjusted Life Expectancy: The in-trial contribution to each patient's quality-adjusted life expectancy will be estimated by multiplying his/her within-trial survival time by the time-weighted average of associated utility weights obtained from the SF-36. For example, the utility value assigned for the first 6 months will be the mean of the baseline and 6 month utility score; the utility for months 6-12 will be the mean of the 6-month and 12-month utility assessments; and so on.

B. Projecting Beyond the Trial for QALYs and Costs: Although the randomized trial will follow patients for 2 years, outcomes pertinent to cost-effectiveness may continue to evolve well after its conclusion. In particular, it is anticipated that most patients will remain alive at the trial's conclusion and that the benefit of PCDT will accrue over the long term, through a reduction in morbidity and costs associated with PTS. Thus, a method is required for converting the observed trial experience into corresponding lifetime quality-adjusted survival and cost figures needed for the incremental cost-effectiveness calculations. Although the use of "within-trial" cost-effectiveness ratios would eliminate the need for extrapolation, this approach would bias our analysis substantially against PCDT given its high up-front cost and the expectation that any quality of life benefits are likely to be sustained. Moreover, lifetime ratios are necessary for comparison with external benchmarks.

To extend the trial results beyond the observed time-frame, we will develop a Markov (state-transition) model (189) in which the principal health states will describe the long-term complications of DVT as defined by the clinical trial (e.g., death, recurrent DVT, venous ulcer, cellulitis, pulmonary embolism). This model will be patterned after previous models developed by the EQOL investigators to project long-term complications, costs, and life-expectancy in patients with chronic coronary disease, acute myocardial infarction, and cerebrovascular disease (190-192). In addition to the ATTRACT Trial itself and published literature, a potential source of cost, transition probability and utility inputs for the model is long-term follow-up results from the Venous Thrombosis Outcomes (VETO) study, a 5 year (2002-2007), multicenter prospective follow-up study of 387 patients with acute symptomatic DVT that is collecting detailed resource use and costs data relating to PTS. We will have full access to the 5 year VETO data through the study's principal investigator, Dr. Susan Kahn (ATTRACT Steering Committee member). Although the primary cost data for

VETO are applicable to the Canadian health care system, they can be converted to approximate U.S. equivalents using Purchasing Power Parities (193). These data will be essential to projecting the incremental costs associated with PTS (stratified by severity level) that are critical to model the long-term QOL impact of PCDT in preventing late DVT complications.

C. Incremental Cost-Effectiveness Analysis: Once the estimates of long-term costs and QALYs have been obtained for each of treatment arm, an incremental cost-effectiveness analysis will be carried out. For this analysis, costs and survival beyond the first year will be discounted at 3% per year according to current standards. Bootstrap analysis will be used to assess the precision of the cost-effectiveness ratios, and the results of the analysis will be presented graphically in the cost-effectiveness plane, including percentages of the distribution falling in the dominant (clinical benefit at lower costs) and dominated (higher costs but no clinical benefit) quadrants. In addition, results from the bootstrap analysis will be presented in the form of cost- effectiveness acceptability curves, which describe the evidence in support of cost-effectiveness across a range of cost-effectiveness thresholds (194-197).

D. Secondary Cost-Effectiveness Analyses: In addition to the pre-specified primary cost-effectiveness analyses, we will perform a variety of exploratory secondary analyses. This will include subgroup analyses to identify cost-effective strategies for specific types of patients and will be based on the pre-specified patient subgroups identified in the clinical protocol.

E. Sensitivity Analyses: Extensive and comprehensive sensitivity analyses, including probabilistic sensitivity analysis on parameters such as Markov model transition rates, will be performed on all key factors in the cost-effectiveness analysis. For factors that are measured empirically during the study, such as QOL and costs, analyses will consider not only mean values but also values that are one standard-deviation removed from the mean and the 95% confidence intervals for the parameters. Less marked variations will also be considered, and one-way and two-way thresholds for indifference between the various strategies will be determined. We will also consider alternative discount rates ranging from 0-7%.

Appendix 14: Study Procedures and Assessments

PROCEDURE	Pre Rand Screening	Pre Rand Baseline	Rand	Initial Tmt	Visit 1 10 days ±3 days	Visit 2 30 days ±7 days	Visit 3 6 mo ±1 mo	Visit 4 12 mo ±1 mo	Visit 5 18 mo ±1 mo	Visit 6 24 mo ±2 mo
Informed Consent	X									
History & Physical	X									
Blood Tests	X(1)				X(2)					
Start AC in both arms	X	X		X						
Rate Leg Pain (3)		X			X	X				
Measure Leg Circumference (3)		X			X	X				
QOL Questionnaire (SF-36, VEINES)		X				X	X	X	X	X
Duplex Ultrasound		X				X		X(4)		
Randomization			**R**							
PCDT/venograms - PCDT arm only				X(5)						
Dispense ECS					X					
Record/report on-serious AEs					X	X				
Record/report serious AEs					X	X	X	X	X	X
Review AC, ECS, Cost Diary					X	X	X	X	X	X
Villalta PTS Scale (3)		X			X	X	**X**	**X**	**X**	**X**
VCSS Scale (3)							X	X	X	X
CEAP Clinical Class (3)							X	X	X	X

(1) CBC with platelets, PT/INR, creatinine; a pregnancy test will be obtained only in women of childbearing potential.

(2) Platelet count to assess for HIT

(3) Assess both legs. NOTE: For bilateral DVT, designate the "index leg" prior to randomization.

(4) The 12-month follow-up Duplex ultrasound will be obtained only in Ultrasound Substudy patients.

(5) Venograms performed immediately before and after PCDT will be obtained only in the Experimental (PCDT) arm patients.

Abbreviations: QOL quality of life; AE adverse event; ECS elastic compression stockings; AC anticoagulation; PCDT pharmacomechanical catheter-directed intrathrombus thrombolysis.

Appendix 15: Unanticipated Problems

From "Adverse Event and Unanticipated Problem Reporting Policy" NHLBI 2/2/09