THE ATTRACT TRIAL

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

MANUAL OF PROCEDURES

Version 3.0

January 23, 2011

TABLE OF CONTENTS

APPENDICES

GLOSSARY OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACR	American College of Radiology
AE	Adverse event
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CDT	Catheter-directed intrathrombus thrombolysis
CEAP	Clinical-Etiologic-Anatomic-Pathophysiologic Classification
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment
CLCS	Core Laboratory for Clinical Studies
CPR	Cardiopulmonary resuscitation
CRF	Case report form
CT	Computed tomography
CV	Curriculum vita
DCC	Data Coordinating Center
DCQ	Data clarification query
DHHS	Department of Health and Human Services
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ECS	Elastic compression stockings
ED	Emergency Department
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-induced thrombocytopenia
HRPO	Human Research Protection Office
ICAC	Independent Central Adjudication Committee

ICAVL	Intersocietal Commission for Accreditation of Vascular Laboratories
ICF	Informed Consent Form
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRIS	Interactive Registration/Randomization System
IVC	Inferior vena cava
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations
LMWH	Low molecular weight heparin
MAHI	Mid America Heart Institute
MDRD	Modification of Diet in Renal Disease
MOP	Manual of Procedures
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
NS	Normal saline
OCOG	Ontario Clinical Oncology Group
OHRP	Office of Human Research Protection
ORCCID	Online Remote Collection of Clinical Information and Data
PCDT	Pharmacomechanical catheter-directed intrathrombus thrombolysis
PE	Pulmonary embolism
PI	Principal Investigator
PT	Prothrombin time
PTS	Post-Thrombotic Syndrome
PTT	Partial thromboplastin time
QOL	Quality of life
rt-PA	Recombinant tissue plasminogen activator
SAE	Serious adverse event
SIR	Society of Interventional Radiology
UP	Unanticipated Problem
UFH	Unfractionated heparin
US	Ultrasound
VCSS	Venous Clinical Severity Score
VTE	Venous thromboembolism

1 INTRODUCTION

The ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) Trial is a Phase III, multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial. 692 subjects with symptomatic proximal deep vein thrombosis (DVT) will be randomized to receive either adjunctive Pharmacomechanical Catheter-Directed Thrombolysis (PCDT) + standard DVT therapy or standard DVT therapy alone in 30-60 U.S. Clinical Centers. The primary outcome measure is the cumulative occurrence of the Post-Thrombotic Syndrome (PTS) over the 24-month follow-up period.

The ATTRACT Trial is sponsored by the National Institutes of Health (NIH) via the National Heart Lung and Blood Institute (NHLBI), and is governed by the terms in NHLBI grant awards U01-HL088476 (to the Clinical Coordinating Center at Washington University in St. Louis, MO) and U01-HL088118 (to the Data Coordinating Center at McMaster University in Hamilton, Ontario). The ATTRACT Trial is registered at http://clinicaltrials.gov under registration number NCT00790335. Activase® (recombinant tissue plasminogen activator, rt-PA) is being used as the Study Drug for ATTRACT under IND 103462 from the Food and Drug Administration (FDA).

This Manual of Procedures (MOP) is designed to describe study flow to ensure that screening, initial evaluation, enrollment, randomization, treatment, and follow-up of all study participants are conducted in a structured and standardized manner. The MOP also details how the data are observed, collected, and recorded. It specifies quality control procedures, defines methods for protecting participant safety and confidentiality of participant information, and describes an operational communication structure for the study. The MOP is a dynamic document that will be periodically amended to reflect Protocol changes and refinement of study procedures. The ATTRACT Trial MOP is written in sufficient detail to enable it to be used both as a critical guide for proper study conduct and as a training manual for new study investigators and coordinators.

2 STAFF ROSTER

Please refer to the ATTRACT Protocol (Appendix 1 and Section 19) for a description of the study's organizational structure and committee responsibilities. Abbreviated contact information for members of the study committees, core laboratories, coordinating centers and other key persons are presented in this section. Detailed contact information for senior study leadership are also presented here. A list of key operational contacts is presented in **MOP Appendix A**.

SENIOR STUDY LEADERSHIP

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kearonc@mcmaster.ca

2.1 Steering Committee

The Steering Committee is the governing and advisory body that is responsible for the overall direction and leadership of the ATTRACT Trial (see Protocol Section 19.1 for a list of specific responsibilities). The Steering Committee includes expert investigators from interventional radiology, vascular surgery, cardiovascular medicine, pulmonary medicine, emergency medicine, hematology, epidemiology, and biostatistics, of whom many serve as investigators at the Clinical Centers. The NHLBI Project Officer and a physician representative of the Society of Interventional Radiology (SIR) Foundation also serve on the Steering Committee.

Meetings of the Steering Committee are held quarterly, with one in-person meeting each year. The group also communicates by e-mail and telephone as needed. Communications for the Steering Committee should be sent to Colleen Kilbourne-Glynn, ATTRACT Project Manager, at the CCC – after review, they will be forwarded to the Chair or the full committee as appropriate.

STEERING COMMITTEE ROSTER

Chair, Steering Committee	Contact Information
Samuel Z. Goldhaber, MD Professor of Medicine Harvard Medical School Brigham & Women's Hospital Boston, MA	Phone: (857) 307-1932 Fax: (857) 307-1955 sgoldhaber@partners.org

Steering Committee Members

David J. Cohen, MD, MSc Director, Cardiovascular Research Professor of Medicine University of Missouri - Kansas City St. Luke's Mid America Heart Institute Kansas City, MO	Phone: (816) 932-4581 Fax: (816) 932-4582 dcohen@saint-lukes.org
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Steering Committee Members (continued)	Contact Information
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Clive Kearon, MB, MRCP(1), FRCP(C), PhD Professor of Medicine McMaster University Juravinski Hospital Hamilton, Ontario (Canada)	Phone: (905) 383-2251 Fax: (905) 574-7625 kearonc@mcmaster.ca
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Steering Committee Members (continued)	Contact Information
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Mahmood K. Razavi, MD Director of Clinical Trials St. Joseph's Vascular Institute Orange, CA	Phone: (714) 744-8795 Fax: (714) 744-8798 mrazavi@pacbell.net
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Suresh Vedantham, MD Professor of Radiology & Surgery Mallinckrodt Institute of Radiology Washington University School of Medicine St. Louis, MO	Office Phone: (314) 362-2923 Pager: (314) 836-1613 Cell Phone: (314) 283-8846 vedanthams@mir.wustl.edu

2.2 Operations Committee

The Operations Committee provides high-level oversight over the daily operations of the ATTRACT research team to ensure optimal coordination of its efforts (see Protocol Section 19.2 for a list of specific responsibilities). Among its responsibilities include a routine review of serious adverse events and major protocol violations. The Operations Committee will also coordinate the initial review of, and make recommendations to the Steering Committee on, all proposals for publications and ancillary studies.

Teleconferences of the Operations Committee are held monthly. Communications for the Operations Committee should be sent to Colleen Kilbourne-Glynn, ATTRACT Project Manager, at the CCC – after review, they will be forwarded to the Chair or full committee as appropriate.

OPERATIONS COMMITTEE ROSTER

Chair, Operations Committee	Contact Information
Suresh Vedantham, MD	Phone: (314) 362-2923
Professor of Radiology & Surgery	Fax: (314) 362-2276
Washington University School of Medicine	vedanthams@mir.wustl.edu

Operations Committee Members

Samuel Z. Goldhaber, MD	Phone: (857) 307-1932
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Harvard Medical School	sgoldhaber@partners.org
Clive Kearon, MB, MRCP(1), FRCP(C), PhD	Phone: (905) 383-2251
Professor of Medicine	Fax: (905) 574-7625
McMaster University	kearonc@mcmaster.ca
Timothy P. Murphy, MD, FSIR, FAHA, FSVMB, FACR	Phone: (401) 444-6105
Professor of Radiology	Fax: (401) 444-6111
Brown University	tmurphy@lifespan.org

2.3 Clinical Coordinating Center (CCC)

The Clinical Coordinating Center (CCC) at Washington University is the primary coordination and communication hub for the study, and will monitor and support the activities at the Clinical Centers (see Protocol Section 19.3). Hence, the vast majority of the communication between the Clinical Centers and the study leadership is expected to flow through the CCC. General mailings, faxes, and other communications to the CCC can be directed to the address below:

ATTRACT Trial Clinical Coordinating Center
Mallinckrodt Institute of Radiology
Washington University School of Medicine
660 S. Euclid Ave., Box 8131
St. Louis, MO 63110
Phone: (314) 747-2379
Fax: (314) 747-1944
attract@mir.wustl.edu

To directly contact the CCC staff member who is best suited to handle a specific query, please use the contact information and responsibility areas of key CCC staff members noted below:

Chair, Clinical Coordinating Center	Contact Information
Suresh Vedantham, MD	Office Phone: (314) 362-2923
Professor of Radiology & Surgery	Pager: (314) 836-1613
Mallinckrodt Institute of Radiology	Cell Phone: (314) 283-8846
Washington University School of Medicine	vedanthams@mir.wustl.edu

CCC Safety Officer	
James R. Duncan, MD, PhD	Phone: (314) 747-6281
Associate Professor of Radiology & Surgery	Fax: (314) 362-2276
Mallinckrodt Institute of Radiology	duncanj@mir.wustl.edu
Washington University School of Medicine	

CCC Staff Members & Contact Information	Responsibility Areas
Melissa Bellovich Special Project Coordinator Phone: (314) 747-2379 bellom@mir.wustl.edu	Investigator Meeting Website and e-newsletter Requests for advertising materials Changes to personnel & contact info
Mary Clare Derfler, RN, MSN Clinical Research Nurse Coordinator Phone: (314) 747-2372 derflerm@mir.wustl.edu	Clinical Center start-up Liaison to Medical Therapy Committee Requests for Study Drug Serious Adverse Event Reporting
David Gibson, BS Core Laboratory for Clinical Studies (CLCS) Phone: (314) 362-7869 Fax: (314) 362-4758 dave@im.wustl.edu	Shipping of Study Drug Confirm receipt of Study Drug
Colleen Kilbourne-Glynn, MA, CCRP Project Manager Phone: (314) 747-2498 kilbourne-glynnc@mir.wustl.edu	Financial and contract issues Liaison to Steering Committee Liaison to Operations Committee
Patty Nieters, RN, BSN Clinical Research Nurse Coordinator Phone: (314) 362-3371 nietersp@mir.wustl.edu	Clinical Center start-up Liaison to Interventions Committee Serious Adverse Event Reporting
Laura Todt, RN, BSN Clinical Research Nurse Coordinator Phone: (314) 747-8951	Clinical Center start-up Regulatory issues Serious Adverse Event Reporting

2.4 Data Coordinating Center (DCC)

The Data Coordinating Center (DCC) for ATTRACT is the Ontario Clinical Oncology Group (OCOG) - Division of Thrombosis, at the Henderson Research Centre at McMaster University in Hamilton, Ontario (Canada). The DCC's primary function is to centrally coordinate the study data management (see MOP Section 10 and Protocol Section 19.4 for specific responsibilities).

Chair, Data Coordinating Center	Contact Information
Clive Kearon, MB, MRCP(1), FRCP(C), PhD	Phone: (905) 383-2251
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Chair, Independent Central Adjudication Committee	Fax: (905) 575-2639
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Chair, Department of Oncology	
McMaster University	
Juravinski Hospital and Cancer Centre	
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Erin McGean Phone: (905) 527-2299, ext. 42656
Data Monitor Fax: (905) 575-2639
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2.5 Vascular Ultrasound Core Laboratory

VasCore, at the Massachusetts General Hospital in Boston, MA, will serve as the Vascular Ultrasound Core Laboratory for ATTRACT (responsibilities listed in Protocol Section 19.3.5).

Chair, Vascular Ultrasound Core Laboratory — Contact Information
Michael R. Jaff, DO, FACP, FACC — Phone: (617) 726-3784
Associate Professor of Medicine — Fax: (617) 724-0371
Harvard Medical School — mjaff@partners.org
Medical Director, Vascular Center
Medical Director, VasCore
Massachusetts General Hospital

VasCore Project Manager
Gail Hadley, RN, RVT — Phone: (617) 726-5552
Technical Director, VasCore — Fax: (617) 724-1977
Massachusetts General Hospital — ghadley1@partners.org

2.6 Health Economic Core Laboratory

The Health Economics and Technology Assessment group at St. Lukes Mid America Heart Institute (MAHI) in Kansas City, MO, will serve as the Health Economic Core Laboratory for ATTRACT (see MOP Section 10.5 and Protocol Section 19.4.3).

Chair, Health Economic Core Laboratory — Contact Information
David J. Cohen, MD, MSc — Phone: (816) 932-4581
Director, Cardiovascular Research — Fax: (816) 932-4582
Professor of Medicine — dcohen@saint-lukes.org
University of Missouri – Kansas City

MAHI Team Members	Contact Information
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Shawn Smitherman Research Associate St. Luke's Mid America Heart Institute	Phone: (816) 932-0394 Fax: (816) 932-4542 ssmitherman@saint-lukes.org

2.7 CCC Committees

Please see Protocol Section 19.3 for information on the respective roles of the Enrollment, Interventions, and Medical Therapy Committees. The committee rosters are presented here:

ENROLLMENT COMMITTEE ROSTER

Committee Member	Role	Phone	E-Mail Address
Lawrence Lewis, MD	Member	(314) 362-9119	lewisl@wusm.wustl.edu
Anthony Comerota, MD	Member	(419) 291-2080	anthony.comerotamd@promedica.org
Timothy P. Murphy, MD	Member	(401) 444-6105	tmurphy@lifespan.org
Gregory Soares, MD	Member	(401) 444-5194	gsoares@lifespan.org
Mark Thoelke, MD	Member	(314) 362-1700	mthoelke@dom.wustl.edu

Dr. Suresh Vedantham also participates on the Enrollment Committee and serves as its Chair.

INTERVENTIONS COMMITTEE ROSTER

Committee Member	Role	Phone	E-Mail Address
Mahmood K. Razavi, MD	Chair	(714) 744-8795	mrazavi@pacbell.net
Mark Garcia, MD	Member	(302) 733-2658	magarcia@christianacare.org
Lawrence Hofmann, MD	Member	(650) 725-5204	lhofmann@stanford.edu
David W. Hunter, MD	Member	(612) 273-2826	hunte001@umn.edu
Robert Lookstein, MD	Member	(212) 241-7409	robert.lookstein@mssm.edu

MEDICAL THERAPY COMMITTEE ROSTER

Committee Member	Role	Phone	E-Mail Address
Heather L. Gornik, MD	Chair	(216) 445-3689	gornikh@ccf.org
Jerry Bartholomew, MD	Member	(216) 444-0825	barthoj@ccf.org
Anthony Comerota, MD	Member	(419) 291-2080	anthony.comerota@promedica.org
Charles Eby, MD	Member	(314) 362-3186	eby@wustl.edu
Michael Militello, PharmD	Member	(216) 444-4194	militem@ccf.org

2.8 Society of Interventional Radiology (SIR) Foundation

Please see Protocol Section 19.3.1 for information on the SIR Foundation's role in ATTRACT.

SIR Foundation Representative	Contact Information
Stephen Kee, MD	Phone: (310) 206-4277
Associate Professor of Radiology	skee@mednet.ucla.edu
UCLA Department of Radiological Sciences	

SIR Foundation Project Manager	
Kathleen Mercure, MHSA	Phone: (703) 460-5596
Clinical Research Manager	kmercure@sirweb.org

2.9 Clinical Centers

See the ATTRACT study website (www.attract.wustl.edu) for an updated list of Clinical Centers.

2.10 Data Safety Monitoring Board

A description of the ATTRACT Trial's DSMB is contained in Protocol Section 17.4 and in the DSMB Charter (available by request). ATTRACT study leadership, site investigators, and site research staff are not permitted to discuss the ATTRACT Trial with any of the DSMB members. Any communications for the ATTRACT Trial DSMB should be directed to Virginia Pichler, RN, PhD, DSMB Executive Secretary, at virginiapichler@westat.com or (800) 518-8474.

Chair, DSMB

Jodi Segal, MD, MPH
Associate Professor of Medicine
Johns Hopkins University

DSMB Members

David Green, MD
Professor of Medicine
Northwestern University

Anna Iltis, PhD
Professor of Bioethics
Saint Louis University

John W. Hirshfeld Jr., MD
Professor of Medicine
University of Pennsylvania

Karim Valji, MD
Professor of Radiology
University of Washington - Seattle

3 TRAINING AND CERTIFICATION

3.1 Overview of Clinical Center Start-Up Requirements

The CCC will ensure that all ATTRACT Clinical Centers have met the following important start-up requirements before approving them to begin enrolling patients.

REQUIREMENT	RESPONSIBLE	MOP SECTION
Designation of Multidisciplinary Team	CCC	3.2
Signed, dated CV – Site PI, Co-Investigators, Pharmacist	CCC	3.2
Medical License - Site PI, Co-Investigators, Pharmacist	CCC	3.2
FDA 1572 Form	CCC	3.2
Federal-Wide Assurance Letter	CCC	3.2
IRB Roster	CCC	3.2
Executed Subaward for NIH-Derived Funds	CCC	3.2
Executed Subaward for Industry-Derived Funds	CCC	3.2
Conflict-of-Interest Disclosure – Site PI, Co-Investigators	Clinical Center	3.3
HIPAA Training Certificate - Site PI & Engaged Team	CCC (PI only)	3.4
IRB Approval Letter for Study Protocol	CCC	3.5
IRB-approved, Stamped Adult ICF & Child Assent Form	CCC	3.5
HIPAA Authorization – if not included in ICF	CCC	3.5
Institutional UFH Nomogram	CCC	3.7
Warfarin Monitoring Plan	CCC	3.7
JCAHO/CAP/CLIA Certification	CCC	3.7
Lab Normal Ranges, Director's Medical License and CV	CCC	3.7
Receive Medical Therapy Certification Letter	**From CCC**	**3.7**
Endovascular Co-Investigator - Board Certification	CCC	3.8
Endovascular Co-Investigator - Experience Statement	CCC	3.8
Choice of AngioJet or Trellis for Initial PCDT	CCC	3.8
Drug Preparation & Accountability Check	CCC	3.8
Receive Endovascular Therapy Certification Letter	**From CCC**	**3.8**
Site Assessment Survey	VasCore	3.9
Qualifying Compression US Exam	VasCore	3.9
Receive Compression US Certification Letter	**From CCC**	**3.9**
Complete Module on PTS Assessment	CCC	3.10
Delegation of Authority/Responsibility Form	CCC	3.12
Review Randomization Training (IRIS) Instructions	DCC	3.11
Complete CRF Training (ORCCID) – E-Learning	DCC	3.12
Receive Site Initiation Approval Letter	**From CCC**	**3.1**

After completion of all requirements above, the CCC will issue a Site Initiation Approval Letter, signed by Dr. Vedantham. Sites may not enroll patients until they have received this letter.

See the Form Submission Guide in **MOP Appendix B** for details on submitting this information.

3.2 General Requirements

Each ATTRACT Clinical Center should field a multidisciplinary research team that includes: 1) an endovascular co-investigator to perform the PCDT procedures; 2) a medical co-investigator to manage anticoagulant therapy; 3) an emergency medicine co-investigator to identify potential patients and coordinate subject screening processes; 4) a vascular ultrasound laboratory co-investigator to identify potential patients and coordinate the acquisition and submission of ultrasound data; 5) a research coordinator; 6) a pharmacist to prepare the Study Drug; and 7) a blinded clinician (physician or nurse) to perform the clinical outcome assessments. Any deviation from this requirement must be approved by Dr. Vedantham. Signed, dated curriculum vitae and medical licenses for each co-investigator, a FDA 1572 Form, the Clinical Center's Federal Wide Assurance Letter, and the Institutional Review Board (IRB) Roster must all be submitted to the CCC. Prior to site initiation, the CCC must also have on file two fully executed subawards between Washington University and the Clinical Center: a) a subaward for the NIH-derived funding component; and b) a subaward for the industry-derived funding component (see MOP Section 12). A copy of the above documents should be kept in the Site Regulatory Binder.

3.3 Conflict-of-Interest Disclosures

Each Clinical Center must have in place a policy and process for identifying and resolving conflicts-of-interest that is compliant with NIH and FDA guidelines. Each investigator must maintain an updated conflict-of-interest disclosure with the Clinical Center's internal review board. If a potential conflict is identified, the Clinical Center must notify Washington University (the primary NIH grantee) of the existence of the potential conflict, its nature, and how it was resolved. Washington University will then notify the NHLBI and FDA of the potential conflict.

3.4 Human Subjects Protection Training

Each individual involved in the design or conduct of research involving human subjects must be trained as stipulated by NIH Notice OD-00-039, release date June 5, 2000 (revised August 25,

2000), http://www.grants.nih.gov/grants/guide/notice-files/Not-OD-00-039.html. If a study member needs to complete this training, this can be done through his/her own institution or through the NIH Office of Extramural Research (http://phrp.nihtraining.com/users/login.php). Prior to site initiation, the site PI's human subjects training certificate must be sent to the CCC. The human subjects training certificates of other key personnel (co-investigators, other physicians that will interact with ATTRACT subjects for research purposes, research coordinators, pharmacists, sonographers) should be placed in the Site Regulatory Binder.

3.5 Institutional Review Board (IRB) Approval

Prior to the initiation of a Clinical Center, the ATTRACT study Protocol must be reviewed and approved by the Center's local IRB, and must subsequently undergo annual IRB review with approval of any amendments. IRB submission documentation, all correspondence with the IRB about the study, contingency letters, and all approval letters should be maintained at the Clinical Center in the Site Regulatory Binder. As a NIH-sponsored study operating with a FDA Investigational New Drug (IND), the ATTRACT Trial is regulated under 45 CFR part 56 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm) and 21 CFR Part 312 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1). The CCC operates as a sponsor-investigator and must regularly report to the NIH and the FDA. For this reason, a copy of all IRB approval letters must be provided to the CCC. To keep all sites working concurrently on the same Protocol version, IRB approval on all amendments should be obtained within 60 days of their posting on the study website (www.attract.wustl.edu). After IRB approval is obtained for amendments, the IRB approval letter and IRB-approved ICF should be submitted to the CCC. The CCC will send the site a Site Conversion Approval Letter that approves the site to begin working on the new Protocol version. The CCC will notify the DCC, and the DCC will convert the site to the new version in the electronic database.

For initial IRB Protocol approval and for amendments where there are significant changes to the informed consent language, each Clinical Center must submit its informed consent form (ICF) draft to the CCC for review and approval before submitting it for local IRB review. The CCC will make every effort to provide review comments on the ICF to the site within 7 days. After a Clinical Center's ICF is approved by the CCC, it may be submitted to the local IRB. After IRB approval is obtained, the IRB-approved, stamped ICF must be submitted to the CCC. Sites will not be initiated until the ICF is approved by both the ATTRACT CCC and the local IRB.

For subjects who are minors, parental informed consent must be obtained along with the child's assent. An IRB-approved, stamped child Assent Form should be provided to the CCC. To assist the Clinical Centers, template ICFs and Assent Forms (in English and Spanish) will be provided to the sites by the CCC, and may be modified to suit the preferences of the local IRB.

3.6 Training for Sizing of Elastic Compression Stockings

BSN Medical is supplying elastic compression stockings for use in ATTRACT patients (MOP Section 7.5). Near the time of site initiation, each research coordinator will be contacted by a local BSN Medical representative to arrange the initial product delivery, discuss the re-order process, and provide a training DVD on the proper sizing, fitting, and donning of the garments. This DVD should be kept at the site for refreshment of training or to train new staff members.

3.7 Certification for Medical Therapy

To maximize the study's ability to accurately assess its primary hypothesis regarding PCDT's efficacy for prevention of PTS, all subjects must receive optimal medical DVT therapy. Prior to site initiation, each Center must be certified by the CCC to provide medical DVT therapy to ATTRACT subjects. This process will be coordinated by the Medical Therapy Committee, and involves submission of the following materials to the CCC research coordinator:

Medical Co-Investigator Credentials - The current, signed, dated curriculum vita and medical license of the medical co-investigator should be submitted to the CCC. This person may be the site PI or a designee, but must be an appropriately trained physician who is experienced with the management of initial and long-term anticoagulant therapy for DVT, and who has an active medical license in the state in which the Clinical Center resides. This individual must oversee the execution of the medical therapy aspects of the study and be responsible for administering standard DVT therapy to most study subjects at that Center over the 2-year follow-up period.

Unfractionated Heparin (UFH) Nomogram – The Clinical Center's institutional nomogram for dosage and monitoring of intravenous UFH, either using anti-factor Xa assays for heparin activity or using aPTT values which correlate to therapeutic anti-factor Xa levels, should be submitted. If no nomogram is available, a descriptive plan for heparin monitoring and dosage adjustment (including therapeutic range for aPTT assay, if applicable) may be submitted, and will be reviewed on a case-by-case basis by the Medical Therapy Committee.

Warfarin Monitoring Plan - A brief written statement detailing the process for monitoring warfarin therapy at the Clinical Center in ATTRACT subjects should be submitted, and should address the following details: the names and credentials of health care providers who will assist with anticoagulation monitoring (physicians, nurses, pharmacists), a description of how PT/INR values will be obtained (e.g., institutional or external laboratory blood draw, point of care testing), the default frequency of INR testing (no less frequent than once every 4 weeks once a stable INR is achieved), and by whom and how the results are communicated to the patient. Whenever possible, the designated medical co-investigator will assume primary responsibility for subjects' long-term anticoagulation management during ATTRACT. Alternative plans for physician oversight of warfarin monitoring should be delineated in the monitoring plan. An example of an acceptable warfarin monitoring plan is provided in **MOP Appendix C**.

Hospital Accreditation and Laboratory Certifications - Proof of hospital accreditation by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) should be provided to the CCC. The clinical laboratory's Clinical Laboratory Improvement Amendment (CLIA) and/or College of American Pathologists (CAP) certifications should also be provided along with a list of normal laboratory values and the laboratory Director's curriculum vita and medical license.

Review Process: When all of the above items have been received by the CCC, the Medical Therapy Committee will review them and provide a recommendation (approve, reject, or request more information) to the CCC. CCC staff will communicate this decision, and any request for additional documentation, to the Clinical Center. Once the Clinical Center is approved by the Medical Therapy Committee and CCC, the CCC will provide a Medical Therapy Certification Letter to the Clinical Center. Clinical Centers may not be initiated until they have received this certification. Questions concerning medical therapy certification may be directed to Dr. Heather Gornik, Chair, ATTRACT Trial Medical Therapy Committee. Appeals on medical therapy certification decisions may be directed to Dr. Suresh Vedantham, Chair, Operations Committee.

3.8 Certification for Endovascular Therapy

To maximize the study's ability to accurately assess its primary hypothesis regarding PCDT's efficacy for prevention of PTS, the PCDT procedures must be performed by qualified physicians who are experienced with endovascular DVT thrombolysis. The designated endovascular co-investigator may be the site PI or a designee, and will perform and/or oversee the performance of the PCDT procedures in the study. Prior to site initiation, the designated endovascular co-

investigator and each physician who will perform PCDT procedures in ATTRACT subjects must be certified by the CCC. This process will be coordinated by the Interventions Committee, and involves submission of the following materials to the CCC research coordinator:

Endovascular Co-Investigator Credentials – Every person who performs PCDT procedures in ATTRACT must be an appropriately trained, board-certified endovascular physician with an active medical license in the state where the site resides. The current signed, dated curriculum vitae, medical licenses, and board certifications of the designated endovascular co-investigator and all physicians who wish to perform PCDT procedures in ATTRACT subjects should be submitted along with a brief statement of prior experience with endovascular DVT therapy that includes, at a minimum, the numbers of: a) endovascular DVT treatments performed for lower extremity DVT and upper extremity DVT (each); b) ultrasound-guided venous access procedures (any type) performed; c) ultrasound-guided popliteal vein accesses performed; d) iliac vein stent placements performed; and e) Trellis PCDT cases (for Centers choosing Technique A) or AngioJet PCDT cases (for Centers choosing Technique B) performed. A form that may be used to document this experience is provided in **MOP Appendix D**.

Choice of PCDT Device: Each site must select either the Trellis (Technique A) or the AngioJet (Technique B) for initial rt-PA delivery in Experimental Arm patients undergoing single-session DVT therapy. The CCC must be informed of this selection prior to site initiation, and the chosen method must be used by all physicians in all patients receiving single-session PCDT at the site. To optimize its ability to troubleshoot, the Washington University site will alternate between Techniques A and B for single-session PCDT at prospectively-defined, 3-month intervals.

Study Drug Preparation and Accountability: Prior to site initiation, CCC staff will review the following information with the site research coordinator and pharmacist: a) plan for Clinical Center receipt and storage of rt-PA; b) documentation of storage conditions; c) Drug Request Form, Investigational Drug Accountability Log, and Packing Slip (MOP Section 4); d) dilution, reconstitution, and dosing of rt-PA per study Protocol; and e) the site's drug destruction policy.

Review Process: When all of the above items have been received by the CCC, the Interventions Committee will review them and provide a recommendation to the CCC (approve, approve with proctoring, reject, or request more information). Per the case-by-case judgment of the Committee, physicians who have not fulfilled all procedural experience criteria may be

allowed to perform PCDT in ATTRACT if proctored by an approved endovascular physician at that site. The nature of the required proctoring will depend upon the specific deficiency that was identified. CCC staff will communicate the decision, and requests for additional information, to the Center. Once the site is approved by the Interventions Committee and CCC, the CCC will provide an Endovascular Therapy Certification Letter to the site. Sites may not be initiated until they have received this certification. Questions on endovascular certification may be directed to Dr. Mahmood K. Razavi, Chair, ATTRACT Interventions Committee. Appeals on endovascular certification decisions may be directed to Dr. Suresh Vedantham, Chair, Operations Committee.

3.9 Training and Certification for Compression Ultrasound

Two types of lower extremity Duplex ultrasound (US) exams will be performed in ATTRACT: a) compression US exams which primarily document the presence and extent of venous thrombus in the proximal lower extremity veins – these will be performed at all Clinical Centers and the data will be submitted **to the DCC**; and b) substudy US exams which involve detailed evaluation of the lower extremity veins for valvular reflux and residual thrombus – these will be performed only at 7 selected "substudy" Clinical Centers and the data will be submitted **to the Vascular Ultrasound Core Laboratory** (VasCore). **MOP Appendix E** summarizes the key differences in the certification process, exam performance, data submission, and minimum acceptability criteria among the different US exams. The two separate processes for becoming certified to perform these two types of US exams in the ATTRACT Trial are both coordinated by VasCore.

Compression Ultrasound Exams

The Clinical Center's vascular US laboratory must complete a Site Assessment Survey (**MOP Appendix F**) and return it to Gail Hadley, RN, RVT, at VasCore. From each participating vascular US laboratory at the site, 1-2 technologists who will take primary responsibility for ensuring the laboratory's proper performance of compression US exams in ATTRACT should submit one bilateral lower extremity venous Duplex US exam (or two unilateral exams) to VasCore. After review, VasCore will provide a recommendation on the laboratory to the CCC (certify, or do not certify). VasCore may also provide feedback to the site regarding any deficiencies in the submitted exam(s). In general, to be qualified, the lab must have at least one sonographer who has recognized certification as a vascular technologist, and must be able to archive US exams for later retrieval. Ideally, the lab should be able to de-identify US exams prior to submission; however, if this is not technically feasible, the CCC may exempt the lab from this requirement provided that the submission of US exams with identifiers is consistent

with the site's IRB-approved ICF and HIPAA Authorization. If the CCC approves the site, the CCC will send a Compression Ultrasound Certification Letter to the site. Sites may not be initiated until they have received this letter. Appeals concerning compression ultrasound certification decisions may be made to Dr. Suresh Vedantham, Chair, Operations Committee.

Substudy Ultrasound Exams

During the first year of subject enrollment in ATTRACT, each Clinical Center's Site Assessment Survey, Year 1 enrollment performance, US exam quality, and data submission performance will be evaluated by the CCC, DCC, and VasCore. Seven Clinical Centers will be subsequently invited by the CCC to participate in an US Substudy. The Centers selected must be accredited by ICAVL or ACR, and the sonographers performing the Substudy US exams must possess recognized certification as vascular technologists. To be certified to perform Substudy US exams, the sonographer must attend a VasCore training session on the performance of these exams at an Investigator Meeting. The sonographer must then submit one bilateral (or two unilateral) lower extremity venous reflux Duplex US exams, using the ATTRACT Substudy US protocol, to VasCore. After review of these materials, VasCore will provide a recommendation to the CCC on whether to certify the site to perform Substudy US exams. The CCC will then send a Substudy Ultrasound Certification Letter to the site. To accommodate staff turnover, alternate arrangements for ultrasound credentialing may be used if approved by VasCore and the CCC. Appeals concerning US Substudy certification decisions may be made to Dr. Suresh Vedantham, Chair, Operations Committee.

Resources: PowerPoint presentations depicting a properly performed compression US exam and a properly performed Substudy US exam will be provided on the ATTRACT study website (www.attract.wustl.edu) Questions concerning US certification should be directed to Gail Hadley, RN, RVT, Technical Director, or to Dr. Michael Jaff, Medical Director, at VasCore.

3.10 Training for Clinical Outcomes Assessment

The integrity of the ATTRACT Trial data depends critically upon the Clinical Centers' ability to ensure that the assessment of PTS in study patients is conducted in a careful, standardized manner by qualified, blinded, nurse or physician examiners. Accordingly, prior to site initiation, each site's designated blinded clinician should undergo standardized training on the PTS assessments that will be used in the study. This may consist of the blinded clinician's attendance at a 30-minute oral presentation and a 30-minute small-group breakout session on

PTS assessment at the Investigator Meeting. To enable refreshment of this training and to provide ongoing training to new staff members, this presentation will be provided on the ATTRACT study website (www.attract.wustl.edu) along with images depicting the various clinical manifestations of chronic venous disease that are assessed in the Villalta PTS Scale, revised CEAP Classification System, and Venous Clinical Severity Score (VCSS) measures. Each Center will also receive a full color, plastic, graphic visual aid depicting the grading of PTS signs for the Villalta PTS Scale. To be permitted to perform PTS assessments in study patients, blinded clinicians who did not attend the Investigator Meeting must attest to having reviewed these posted website presentations.

3.11 Training for Randomization (IRIS)

Randomization (treatment allocation) of subjects in the ATTRACT Trial will be centralized and is coordinated by the DCC. Before site initiation and prior to randomizing any subjects, each user must review the complete IRIS randomization instructions (document with "screen shots") that may be accessed via the ATTRACT study website (www.attract.wustl.edu). To enable refreshment of this training and to provide training to new staff members, IRIS randomization instructions will continue to be available on the ATTRACT website throughout the study.

3.12 Training for Electronic Case Report Form Submission (ORCCID)

Prior to site initiation, each investigator, coordinator, and/or designated personnel must undergo training on the use of the Online Remote Collection of Clinical Information and Data (ORCCID) system for web-based remote data entry. Before entering data on any case report forms (CRFs) via ORCCID, each user must subsequently complete all components of the online training module (E-Learning) for the ORCCID system. The E-Learning module may also be useful as an ongoing reference for implementation of data entry tasks, and may be repeated at any time.

Prior to site initiation, the Clinical Center must submit a Delegation of Authority/Responsibility Form (**MOP Appendix G**) to the CCC. The CCC will transmit this form to the DCC. The DCC will then provide each site PI, research coordinator and/or designated personnel with log-ins and temporary passwords in order to access both the IRIS and ORCCID systems. Users should complete the E-Learning within 5 business days of receiving their log-in information. The DCC will regularly notify the CCC of users that have successfully completed the E-Learning to enable the CCC to proceed with site initiation. Clinical Center personnel will have 7 days to

change their temporary passwords to a confidential password. Passwords will need to be updated every 90 days. The system will alert the user to this requirement. In addition, a remote data entry manual is available in ORCCID for online viewing and is printable in PDF format.

4 STUDY DRUG (ACTIVASE®)

4.1 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 $\leq$ 30 degrees Celsius (86 degrees Fahrenheit), or under refrigeration at 2-8 degrees Celsius (36-46 degrees Fahrenheit), 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.

4.2 CLCS Receipt, Inventory, and Storage of Study Drug

Activase® 50 mg vials will be provided by Genentech to the CCC for use in ATTRACT. CCC staff will monitor the progress of enrollment at the Clinical Centers, review and approve site requests for Study Drug re-supply, and notify Genentech accordingly. Genentech will then ship the Activase® 50 mg vials to the Core Laboratory for Clinical Studies (CLCS) at the Washington University School of Medicine. Activase® will be supplied as a sterile lyophilized powder in 50mg vials containing vacuum, labeled "For Investigational Use Only, The ATTRACT Study".

When the CLCS receives Study Drug, CLCS staff will confirm that it is properly labeled as being for research only and record the Lot Number, the date of shipment receipt, the expiration date of Study Drug, the number of vials listed on the packing slip, the actual number of vials received, and the condition of the package on arrival (intact or damaged) on the CLCS Investigational Drug Accountability Log (**MOP Appendix H**). This Log will maintain a balance of all vials stored at the CLCS based on Lot Number. There is one Lot Number per form. This form will then be faxed to Genentech at (866) 817-0365 to confirm receipt.

CLCS staff will store the Study Drug in a locked temperature-controlled (2-8º Celsius) room per the Activase® package insert. The room's temperature is continuously tracked on a temperature wheel that is closely monitored by Washington University Protective Services personnel. If a temperature failure occurs, security staff in the computer room will notify the CLCS staff immediately by pager. The CLCS will diligently record all receipt and storage of the Study Drug.

4.3 Study Drug Ordering Process

For most Clinical Centers, the initial shipment of Activase® to the Center from the CLCS will consist of 4 vials. When additional Study Drug is needed, the site should fax a Drug Request Form (**MOP Appendix I**) to the CCC at (314) 747-1944. In general, sites should always have enough Study Drug on site to treat at least 2 patients. The CCC will monitor each site's subject enrollment rate, review the request, approve the distribution of additional Study Drug to the site (if appropriate), and forward the Drug Request Form to the CLCS. The CLCS will then express mail the Study Drug to the site per request. The CCC will also carefully monitor overall study enrollment and the CLCS inventory in order to project future needs for Study Drug. When CLCS re-supply is needed, CCC staff will e-mail a request to Genentech. Whenever possible, 2 weeks advance notice will be provided to Genentech to supply the requested drug to the CLCS.

4.4 Distribution of Study Drug to the Clinical Centers

When directed by CCC staff, the CLCS will ship Study Drug to authorized personnel at the Clinical Centers using Federal Express overnight service. The Study Drug will be sent in a Styrofoam cooler with a refrigerant pack to prevent extreme high temperatures during shipment. Drug shipments will be recorded by CLCS staff on a customized ATTRACT Packing Slip (**MOP Appendix J**). Specifically, the CLCS will record the date of the shipment, the receiving Clinical Center's name and Clinical Center Number, the number of vials shipped, the Lot Number, the Study Drug expiration date, the Federal Express tracking number, and the initials of the CLCS staff person packing the shipment. The original Packing Slip will be sent to the Clinical Center along with the Study Drug, and a copy will be filed in a site-specific Drug Shipment Binder at the CLCS that specifically documents all drug shipments to that Clinical Center. CLCS staff will also record the shipment details on the CLCS Investigational Drug Accountability Form.

4.5 Drug Accountability at the Clinical Centers

Once received at the site, the pharmacist or coordinator should check the Drug Request Form against the Packing Slip and record the Study Drug receipt on the site's Investigational Drug Accountability Log (**MOP Appendix K**). If there is any discrepancy, the Clinical Center should contact the CLCS at (314) 362-7869 to resolve the issue. The Clinical Center should fax the updated Investigational Drug Accountability Log to the CLCS at (314) 362-4782. The CLCS will file the faxed Investigational Drug Accountability Log in the site-specific Drug Shipment Binder. The CLCS will also acknowledge the confirmation of receipt of the Study Drug at the site by checking the last column on the Packing Slip that is marked "For CLCS Use Only".

4.6 Reconstitution and Dilution of Activase®

Please refer to the Activase® Investigator Brochure; the Activase® package insert; and Protocol Section 6.2, Section 7.3.4, and Appendices 4-6. Also use the following guidelines:

1. Activase® must be reconstituted with Sterile Water for Injection, USP, to 1 mg/mL.

2. After reconstitution, further dilution of Activase® must be done with Normal Saline. Do not use other infusion solutions (e.g. Sterile Water for Injection, USP, or preservative-containing solutions) for further dilution. Before dilution or administration, the Activase® should be visually inspected for particulate matter and discoloration.

3. Excessive agitation during dilution should be avoided. Mixing of Activase® should be accomplished with gentle swirling and/or slow inversion.

4. No other medication should be added to Activase® infusion solutions.

5. Any unused Activase® infusion solution should be immediately discarded.

6. Each use of Activase® must be recorded in the site Investigational Drug Accountability Log.

4.7 Study Drug Expiration and Destruction

If Study Drug expires, or is damaged upon receipt or initiation of use (e.g. dropped), at either a Clinical Center or at the CLCS, it should be discarded per the institution's drug destruction policy. In this case, the Clinical Center or CLCS should record this in the Investigational Drug Accountability Log, specifically noting the date, whether the drug was destroyed and if so the reason for destruction, the balance forward, the Lot Number, the Study Drug expiration date, and the recorder's initials. If the recording was done at a Clinical Center, this form should be

faxed to the CLCS at (314) 362-4782. The CLCS will file this form in the site's Drug Shipment Binder, and will also record the information in the CLCS Investigational Drug Accountability Log.

4.8 Record Keeping

As Activase® is being used under IND 103462 from the FDA, stringent record keeping at the Clinical Centers to track all ordering, receipt, use, expiration, and destruction of the Study Drug is mandatory. The Investigational Drug Accountability Log and all Drug Request Forms should be maintained securely at the site. This documentation will be audited at site monitoring visits performed by CCC staff, NHLBI, and/or FDA. An example of the documentation needed for one "cycle" of drug request, distribution, receipt, and use or destruction is provided below:

STEP	DOCUMENTATION	DONE BY
1. CCC Requests Drug from Genentech	E-Mail to Genentech	CCC
2. CLCS Receives Drug from Genentech	CLCS Investigational Drug Accountability Log Entry	CLCS
3. Clinical Center Requests Drug from CCC	Drug Request Form Faxed to CCC	Clinical Center
4. CCC Approves Drug Request	Drug Request Form Forwarded to CLCS	CCC
5. CLCS Sends Drug to Clinical Center	Packing Slip Completed and Enclosed with Drug	CLCS
6. CLCS Sends Drug to Clinical Center	CLCS Investigational Drug Accountability Log Entry	CLCS
7. Clinical Center Receives Drug from CLCS	Investigational Drug Accountability Log Entry	Clinical Center
8. Clinical Center Uses Drug in Patient	Investigational Drug Accountability Log Entry	Clinical Center
9. Clinical Center Destroys Unused Drug	Investigational Drug Accountability Log Entry	Clinical Center

5 SCREENING & ENROLLMENT

5.1 Patient Confidentiality (HIPAA)

The Health Insurance Portability & Accountability Act (HIPAA) provides guidelines for research personnel regarding protection of participant confidentiality. For information on HIPAA, site investigators should review information provided in *Impact of the HIPAA Privacy Rule on NIH Processes Involving the Review, Funding, and Progress Monitoring of Grants, Cooperative Agreements, and Research Contracts* (http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html) and *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*, NIH Publication 03-5388 (http://privacyruleandresearch.nih.gov).

All ATTRACT Trial personnel must strictly adhere to HIPAA guidelines. At each Clinical Center, ATTRACT participants should be informed what safeguards are being taken to protect the privacy of their health information. In most Clinical Centers, patients may be informed that with

the exception of the Medical Billing Release Form, in which the participant's signature will authorize the Health Economic Core Laboratory at MAHI to use his/her identifying information to collect hospital billing records to assess the cost-effectiveness of PCDT (see **MOP Appendix L**), all identifiers will be removed from his/her data and materials sent to the CCC, DCC, and Core Laboratories. Except for imaging exams submitted by Centers that are technically unable to de-identify them, study participants will be identified by a study-specific Subject Identification Number only. Any information provided by the CCC to industry partners (to keep them abreast of overall study progress and relevant serious adverse events) will be completely de-identified.

A signed HIPAA Authorization Form must be obtained from each participant unless this information is already incorporated into the Clinical Center's ICF. The HIPAA Authorization Form describes participant and data confidentiality associated with the study. A blank copy of this form should be kept in the Site Regulatory Binder and the signed HIPAA Authorization Form for each individual patient should be kept in the Patient Binder along with the signed ICF.

5.2 Site-Specific Enrollment Plan

Each site principal investigator must place high priority upon pro-actively crafting and internally communicating a site-specific plan for screening potential subjects for the ATTRACT Trial. This plan should explicitly address the following challenges which have reduced subject accrual in previous DVT thrombolysis trials: a) the need to identify potential subjects within 2 weeks of DVT symptom onset; b) the fact that existing clinical referral pathways tend to identify only the most severely affected DVT patients who have progressed symptomatically or anatomically after receiving anticoagulation alone as initial therapy – but these patients are often unwilling to be randomized and are often referred beyond the 2-week window; and c) the numerous study exclusion criteria – as the failure of initial screens to meet study eligibility criteria can diminish enthusiasm for the study among referring physicians, it is important to periodically reassure them that this is entirely expected and that their continued screening efforts are very worthwhile.

For these reasons, the site-specific enrollment plan should focus upon identifying DVT patients at their initial point-of-contact with health care personnel at each Center. It is expected that the ATTRACT physician co-investigators from the vascular ultrasound laboratory and emergency department, who are best attuned to the workflow considerations in their own areas, will work closely with the site principal investigator to develop this plan as a primary study responsibility.

Incorporation of ATTRACT Trial screening into hospital-wide DVT treatment algorithms (or at least achievement of hospital-wide trial awareness) should be actively sought, when possible.

A successful enrollment strategy will minimize the study's burden upon clinical personnel who are not part of the research team. As a general rule, such personnel should be asked to identify potential subjects, but the time-consuming burden of establishing patient eligibility for the study should be shouldered by the research team. Attempting to confer additional responsibilities upon clinical personnel will deter them from notifying the research team about the patient. Patient recruitment strategies and materials should be approved by the local IRB. Some suggestions for incorporating ATTRACT screening into the daily workflow are provided here:

Vascular Ultrasound Laboratory: The most effective method of screening is likely to be to create an electronic or automated method of reviewing the results of all venous ultrasound studies on a daily basis. Arrangements should be also made with the vascular ultrasound laboratory to notify the ATTRACT research team of any patient in whom lower extremity DVT is diagnosed. A 1-page document or flyer that specifies how to notify the ATTRACT research coordinator and/or investigator with a minimum of effort should be clearly written in large bold type and posted prominently in the laboratory. This sheet should encourage the sonographer to mention ATTRACT to the patient's physician when notifying him/her of the ultrasound results. To enable identification of DVT cases that were not relayed to ATTRACT personnel during normal workflow, sonographers and other staff should be asked to "flag" all DVT exams for periodic review by the vascular ultrasound laboratory co-investigator. The patient's physician may then be contacted to ask permission for the research team to approach the patient.

Emergency Department (ED): Arrangements should be made between the ATTRACT research team and ED staff to encourage routine screening for the study in a manner which minimizes disruption to ED workflow. As in the vascular ultrasound laboratory, a 1-page document or flyer that specifies how to notify the ATTRACT research team of a potential subject with a minimum of effort should be posted prominently. The document should instruct ED physicians to immediately start standard DVT therapy, to ask patients if they are willing to be contacted by ATTRACT staff to discuss the study, and (if yes) to immediately notify the ATTRACT research team. The ATTRACT research team should be aware of the ED's unique workflow challenges and try to respond in the shortest time frame possible. Prior to study start-up, the research

team should discuss with the ED how best to enable ATTRACT subjects to be captured while still maintaining the ED's ability to rapidly determine the admission disposition of DVT patients.

Pharmacy: The Clinical Center may choose to identify potential participants by "flagging" the pharmacy records of patients who are prescribed heparin or warfarin as potential ATTRACT subjects. This list of patients may be provided to the ATTRACT research coordinator to determine if any patients are eligible for the study. The patient's physician must first be contacted to request permission to discuss the study with the potential participants.

CCC Backup: Posted ATTRACT materials should instruct staff to call the CCC at 1-866-974-CLOT (2568) as a backup mechanism if they cannot immediately reach the local ATTRACT research team. The caller should leave a message stating that a potential subject has been identified, along with the name and contact information of the caller and the patient's physician (patient identifiers should not be provided). CCC staff will check this telephone line every 24 hours and follow-up to connect the site's research coordinator with the caller or physician.

Resources: Printed ATTRACT Trial advertising materials (brochure and poster) and a protocol eligibility card will be provided to each Clinical Center upon site initiation. To re-order these materials, contact Melissa Bellovich, ATTRACT Project Coordinator. Tips for successful enrollment will be posted on the ATTRACT website (www.attract.wustl.edu) and included in a monthly e-newsletter. A Recruitment Strategy Resource Guide has been developed and should be considered required reading for all site investigators and coordinators. For questions about patient enrollment, contact CCC staff or Dr. Suresh Vedantham, Chair, Enrollment Committee.

5.3 Screening Log

A record of all patients who are screened for the ATTRACT Trial and meet the study Inclusion Criterion but who are not enrolled should be maintained in a Screening Log. Acceptable entries must document subject status with respect to all exclusion criteria that do not require additional testing to evaluate, and his/her willingness to participate. The paper Screening Log should be faxed monthly to the DCC at (905) 575-2639 (**MOP Appendix B**). A copy of the Screening Log should also be kept in the Site Regulatory Binder. No patient identifiers should be provided on the Screening Log. Screened patients that meet the study Inclusion Criterion but who are not subsequently enrolled should be identified by a sequential Screening Identification Number consisting of the letter "S" followed by a 3-digit number (i.e. S001, S002, S003, etc.).

5.4 Screening Procedures Prior to Obtaining Informed Consent

When a potential subject becomes known to the Clinical Center's ATTRACT research team:

1. Review the potential participant's medical records, laboratory tests, and imaging studies to determine if he/she must clearly be excluded from the study, either by a) clear failure to meet the study Inclusion Criterion (e.g. ultrasound clearly showing isolated calf DVT without proximal extension); or b) clear fulfillment of one or more study exclusion criteria. Although most of the exclusion criteria can be assessed prior to approaching the participant, it is important to remember that any additional testing to assess participant eligibility (such laboratory and pregnancy tests (Exclusion Criteria #9, #10, and #16)) may not be performed until informed consent is obtained and documented.

2. If the patient clearly must be excluded, complete the Screening Log entry as noted in MOP Section 5.3. Because description of the population characteristics of non-included patients is an important part of evaluating the study's external validity, all listed eligibility criteria that do not require additional testing should be assessed and documented in the Screening Log even if it becomes clear that the patient will not qualify to participate.

3. If the patient still appears to be eligible, his/her physician should be contacted by the research coordinator or investigator to determine if he/she is willing to enroll the patient in the study. If so, and if the patient has a history of a mild-moderate allergic reaction to iodinated contrast, the physician should be asked if he/she would be comfortable with the patient treated with PCDT under steroid pre-medication (if randomized to PCDT). If yes, the patient is still eligible. At this point, the patient's physician should query the patient as to whether he/she is willing to speak with the research team about the study.

4. If the answer is yes, then the research team may proceed with the informed consent process described below. If the answer is no, the patient should not be approached. The patient's decision not to consent should be documented on the Screening Log.

5.5 Informed Consent

As required by CFR 45 Part 46.117, a signed informed consent form (ICF) document must be obtained prior to enrollment or the performance of protocol-driven screening tests or procedures for all patients in the ATTRACT Trial. Permission must be obtained from the potential subject's

physician before initiating an informed consent discussion. The study investigator or coordinator should initially ask the potential participant open-ended questions to assess his/her level of comprehension. Cognitively impaired persons should not be offered participation in the study. The study investigator or coordinator should provide a detailed explanation of the study and the ICF to the prospective participant, and should specifically discuss the nature of the study, the duration of subject participation, randomization and blinding, study procedures, visit obligations, the importance of compliance, and potential risks, benefits, and alternatives to participation. The research team member should allow ample time for the prospective participant to carefully read the ICF and have any questions answered. The ICF should be provided to the subject in a certified translation of his/her native language. The informed consent process should always be conducted in a non-coercive manner. Every potential subject should know that he/she is not obligated to participate, that there is no penalty for non-participation, and that his/her medical care will not be compromised if he/she chooses not to participate or later withdraws.

It is important to remember that both the informed consent process and the ICF itself represent teaching tools for the research participant, and that the signing of an ICF does not constitute the entire process of informed consent. ATTRACT Trial personnel should provide opportunities for the subject to have questions answered throughout the duration of his/her study participation.

The ICF should be written in lay language rather than with scientific or legal terminology. All ICF documents for ATTRACT must contain the required elements stipulated in 45 CFR 46.116. Informed consent regulations are administered by the Office of Human Research Protections (OHRP). The OHRP website (http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm) provides a number of tips to guide investigators in developing informed consent documents. The Code of Federal Regulations (CFR) is also accessible on this website for further review. If there are significant updates to the ATTRACT Protocol or new medical information is learned that may impact a patient's decision to participate, participants may need to be re-consented during the study. If a new informed consent is required, the process is repeated; however, the old informed consent is kept as a source document of the original informed consent process. The site principal investigator or designee and the study participant must each sign and date the ICF. The study participant should be provided with a copy of the signed and dated ICF. The original signed ICF should be placed in the Patient Binder at the site by the research team. The informed consent discussion should be briefly documented in the patient's medical record.

5.6 Informed Consent in Children

The ATTRACT Trial includes young people starting at 16 years of age. As per 21 CFR 50, children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted." Although the terms "minor" and "child" may be used interchangeably in conversation, legally there are important differences. Emancipated minors, although not at the state age of adulthood, are legally capable of providing informed consent. Each ATTRACT study team must know its state law as to the age when a young person may execute his/her own informed consent (often referred to as the age of majority).
In ATTRACT, children who fulfill the eligibility criteria may be enrolled provided that the informed consent of one parent is obtained and the child provides his/her signed Assent. As Washington University's Human Research Protection Office (HRPO) has defined ATTRACT as research involving greater than minimal risk but presenting the prospect of direct benefit to the child (45 CFR 46.405), the ICF template that was provided to the Clinical Centers by the CCC does not require the signature of both parents. However, the signatures of both parents should be obtained when it is possible to do so. When an Assent Form is used, copies should be given to the participant and parent(s) and the process should also be documented in the medical record. The original signed Assent Form should also be kept in the Patient Binder at the site.
The NIH policy on inclusion of children in research is available at the following website: http://grants.nih.gov/grants/funding/children/children.htm. When a research patient reaches his/her state's age of majority, he/she should be re-consented on the site's adult ICF.

5.7 Completion of Eligibility Assessment

Once informed consent has been obtained, the research team may complete the assessment of patient eligibility as described in study protocol Section 4.4. In judging each eligibility criterion, please observe the clarifications in MOP Sections 5.8 and 5.9 below. The Screening Log entry should be completed for non-participating patients after assessment of all eligibility criteria.

5.8 Inclusion Criterion

All patients must meet the following subject Inclusion Criterion in order to participate:

Symptomatic proximal DVT involving the iliac, common femoral, and/or femoral vein.
Clarification: Involvement of any one, or more than one, of the above vein segments is sufficient to meet the Inclusion Criterion. The term "femoral vein" (previously known as the

"superficial femoral vein") refers to the deep thigh vein that is the cephalad continuation of the popliteal vein. For purposes of study eligibility, the most caudal aspect of the femoral vein is the point at which it passes through the adductor (Hunter's) canal. Therefore, any patient with symptomatic proximal DVT that extends above the adductor canal meets the Inclusion Criterion. It is also important to realize that involvement of the popliteal and/or calf veins does NOT exclude the patient provided that the iliac, common femoral, and/or femoral vein(s) are involved.

5.9 Exclusion Criteria

Patients meeting <u>any one (or more)</u> of these Exclusion Criteria are not eligible for the study:

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. <u>In the index leg:</u> established PTS, or previous symptomatic DVT within the last 2 years.
   <u>Clarification:</u> In all patients, a careful medical history should be taken with specific reference to the status of the leg with the index DVT prior to the current episode. Patients who have symptoms in that leg that are felt to be likely related to chronic or previous DVT should not be enrolled. Patients with chronic venous disease and no DVT history are eligible.
4. <u>In the contralateral (non-index) leg</u>: symptomatic acute DVT a) involving the iliac and/or common femoral vein; <u>or</u> b) for which thrombolysis is planned as part of initial therapy.
5. Limb-threatening circulatory compromise.
   <u>Clarification:</u> A painful and "massively" swollen leg may be seen in many patients with acute iliofemoral DVT and should not, by itself, exclude the patient. However, if the patient is truly felt to have acute circulatory limb threat, then enrollment would not be appropriate.
6. PE with hemodynamic compromise (i.e., hypotension).
   <u>Clarification:</u> Hypotension is defined as a systolic blood pressure below 90 mm/Hg.
7. Inability to tolerate PCDT procedure due to severe dyspnea or acute systemic illness.
   <u>Clarification:</u> As in routine clinical practice, the medical history and physical exam should include assessment of the patient's ability to tolerate PCDT, which may involve up to four procedure sessions with sedation and prone positioning. However, dyspnea or oxygen desaturation which is easily reversed with provision of supplemental oxygen by nasal cannula, or mild/moderate systemic illness, should not exclude the patient in most cases.
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).
    Clarification: An estimated Glomerular Filtration Rate (eGFR) calculator is available at this link: (http://www.nephron.com/cgi-bin/MDRD_GFR.cgi). The Modified Diet in Renal Disease (MDRD) formula is listed here and in the Confirmation of Eligibility Form: 186 x serum creatinine (mg/dL)$^{-1.154}$ x Age $^{-0.202}$ x 0.742 if female and x 1.21 if African descent.
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 > 180 mmHg or diastolic > 105 mmHg).
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 thienopyridine 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).
    Clarification: If the patient lives distant from the Clinical Center but is willing to return for follow-up visits and has a local physician that will assist the medical co-investigator with meeting study requirements over the 2 years of follow-up, the patient should be enrolled.

5.10 Eligibility Waiver Process

Eligibility waivers will not be granted except in the most unusual of circumstances, but may be addressed to Dr. Suresh Vedantham, ATTRACT Trial Principal Investigator, at the CCC. Any waiver granted will be subsequently reviewed by the Operations Committee.

6 BASELINE ASSESSMENT & RANDOMIZATION

6.1 Pre-Randomization Medical DVT Therapy

Most DVT patients approached for enrollment in ATTRACT will have already been started on anticoagulant therapy. If a patient is receiving UFH, enoxaparin, dalteparin, or tinzaparin with appropriate therapeutic dosing, it may be continued. If the dosing is not appropriate for acute DVT treatment, the dose should be adjusted per Protocol Section 6.1.1. Low molecular weight heparin (LMWH) doses may need to be adjusted in patients with impaired renal function. If a patient is receiving fondaparinux prior to enrollment, this medication must be transitioned to either intravenous UFH or one of the above LMWHs.

Upon enrollment, warfarin should be temporarily held, pending the outcome of blood testing (for INR determination) and randomization. Subjects with an INR > 1.6 may require reversal of anticoagulation if randomized to the Experimental Arm (see protocol Section 7.3.2). If the patient is randomized to the Control Arm, warfarin therapy may be immediately resumed using the dosing and monitoring guidelines described in Protocol Section 6.1.2 and Section 7.2.
If anticoagulation was not initiated prior to enrollment in ATTRACT, therapy should be initiated immediately upon enrollment to avoid delay in necessary standard medical treatment for acute DVT. As delineated in Protocol Section 6.1.1, the subject may receive intravenous UFH or one of the above LMWHs. UFH should be dosed according to the site's approved UFH nomogram.

6.2 Baseline Assessment

Before randomization, all patients will undergo a Baseline Assessment (see Protocol Sections 4.4 and 4.5) that will reflect the patient's status just before randomization.

The Baseline Assessment will consist of the following elements:

- Patient demographics
- Medical history
- Physical examination (to include height and weight) and vital signs
- Review of diagnosis of qualifying episode of DVT
- Laboratory assessments (unless already done within 3 days prior to randomization)
- Completion of questionnaires (QOL & Leg Pain Severity – both legs) (MOP Section 8.5)
- Calf circumference measurement (both legs) (MOP Section 8.6)

- Villalta PTS scale – (subject and blinded clinician, both legs) (MOP Section 8.6)
- Venous Duplex ultrasound of the index leg (unless already done within 5 days prior to randomization)

Important: The results of baseline assessments should be reviewed before randomization. If the hemoglobin < 9.0 mg/dl, the platelets < 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.

Documentation of Baseline Assessment

The following data elements and support documentation become due once the Baseline Assessment has been completed:

- Baseline Form
- Baseline Compression Ultrasound local report
- Compression Ultrasound Form
- Venogram local report, if performed
- CT Venogram local report, if performed
- Leg Pain Severity Form (subject)
- Villalta PTS (Symptoms) Form (subject)
- Quality of Life Questionnaire (subject)
- Villalta PTS (Signs) Form (blinded clinician)
- Laboratory reports

6.3 Stratification and Preparation to Randomize

As noted in Protocol Section 4.1, the "index leg" that will be used in the study outcome analyses must be designated prior to randomization for all patients with bilateral DVT. Subjects should be randomized as soon as possible after the Baseline Assessment is completed, and ideally when PCDT can be performed within 24 hours. In Experimental Arm subjects, PCDT should be performed within 3 days after randomization. Prior to randomization, subjects will be stratified by two factors: 1) by the highest anatomic extent of DVT (whether or not it involves the common femoral vein and/or iliac vein) – research coordinators should be familiar with the patient's imaging results and be prepared to enter this information into the IRIS online randomization system (MOP Section 6.4); and 2) by the Clinical Center at which they are treated – each site will be assigned a unique identifying Clinical Center Number at start-up.

6.4 Randomization

Subject randomization is completed by Clinical Center personnel who will access the DCC's web-based Interactive Registration/Randomization System (IRIS) via a link from the ATTRACT study website's homepage (www.attract.wustl.edu). Clinical Center personnel must use the subject screen to answer all eligibility criteria, document the date informed consent was obtained and the ICF version date, document pregnancy test results (if applicable), document the date of the baseline compression ultrasound and laboratory assessments, select the strata, and then the system will provide a unique Subject Identification Number and treatment allocation. Once randomization is completed, site personnel will print the Confirmation of Eligibility Form, the investigator will sign and date this form, and the site coordinator will fax the signed copy to the DCC within 24 hours. The original Confirmation of Eligibility Form should be sent by courier to the DCC (see **MOP Appendix B** for details). The DCC will verify the information and build an individual subject schedule electronically which will allow Clinical Center personnel to begin data entry for that subject in the ORCCID Electronic Data Capture system within 24 hours. Complete IRIS randomization instructions (document with "screen shots") is available in the Investigator Resources section of the ATTRACT study website.

6.5 Subject Identification (ID) Number

Each randomized patient will have a unique, 7-digit Subject Identification Number which combines the 4-digit Clinical Center Number (assigned prior to site initiation) and the 3-digit Subject Number (sequentially numbered starting with 001 for the first randomized patient at each Center). For example, the first eligible, consenting, randomized subject at Clinical Center 4001 would have 4001001 as his/her Subject ID Number. The first eligible, consenting, randomized subject at Clinical Center 4002 would have 4002001 as his/her Subject ID Number.

The composition of the Subject ID Number is depicted here: |___|___|___|___| |___|___|___|

Center Number **Subject Number**

7 DVT TREATMENT

7.1 Summary of Allowed Treatments

TREATMENT	CONTROL ARM PATIENTS	PCDT ARM PATIENTS
Initial Anticoagulation	**Required**	**Required**
Therapeutic UFH	Allowed	Allowed
Subtherapeutic UFH	Prohibited	Allowed during rt-PA infusion
Enoxaparin	Allowed	Allowed
Dalteparin	Allowed	Allowed
Tinzaparin	Allowed	Allowed
Fondaparinux, Dabigratran	Prohibited	Prohibited
Long-Term Anticoagulation	**Required**	**Required**
Warfarin	Allowed	Allowed, hold before & during PCDT
LMWH Monotherapy	2nd line only	2nd line only
Fondaparinux, Dabigatran	2nd line only	2nd line only
Antiplatelet Agents	**Discouraged**	**Discouraged**
Aspirin, NSAIDs, Clopidogrel	Discouraged	Discouraged
Other Thienopyridines	Prohibited early, discouraged late	Prohibited early, discouraged late
Glycoprotein IIb/IIIa Antagonists	Prohibited early, discouraged late	Prohibited early, discouraged late
Elastic Compression Stockings	**Strongly Encouraged**	**Strongly Encouraged**
Initial PCDT (within 3 months)	**Prohibited except limb threat***	**Required initially, may repeat up to twice**
Trellis PCDT or AngioJet PCDT	Prohibited except limb threat	Required if good popliteal inflow, no IVC clot
Infusion-First PCDT	Prohibited except limb threat	Required if poor popliteal inflow or IVC clot
Rheolytic Thrombectomy	Prohibited except limb threat	Allowed for residual clot after initial PCDT
Aspiration Thrombectomy	Prohibited except limb threat	Allowed for residual clot after initial PCDT
Balloon Maceration	Prohibited except limb threat	Allowed for residual clot after initial PCDT
Additional rt-PA via Trellis	Prohibited except limb threat	Allowed for residual clot after initial PCDT in Technique A patients only
Additional rt-PA via AngioJet	Prohibited except limb threat	Allowed for residual clot after initial PCDT in Technique B patients only
Additional rt-PA via Infusion CDT	Prohibited except limb threat	Allowed for residual clot after initial PCDT and adjunctive measures have been used
Balloon Angioplasty	Prohibited except limb threat	Allowed for residual venous obstruction
Stent Placement	Prohibited except limb threat	Allowed for residual obstruction in the common femoral vein, iliac vein, and/or IVC
Insert & Retrieve IVC Filter	Prohibited except limb threat	Allowed for iliofemoral DVT before use of Trellis PCDT or AngioJet PCDT
Off-protocol clot removal methods	Prohibited except limb threat	Prohibited except limb threat
Late Endovascular Therapy*	**Strongly Discouraged***	**Strongly Discouraged***
PCDT $\pm$ above adjuncts*	Severe venous disease only	Severe venous disease only
Stent Placement (without PCDT)*	Severe venous disease only	Severe venous disease only
Saphenous Ablation*	Severe venous disease only	Severe venous disease only
IVC Filter	AC contraindication or failure	AC contraindication or failure

***** Per Protocol Sections 6.2.8 and 12.4, Dr. Vedantham should be notified and the assessments outlined in the MOP Section 8.4 Table should be performed before performing the procedure, if possible.

7.2 Tips for Providing PCDT Therapy

Clarification of Popliteal Inflow Criterion for PCDT Technique Selection

1. **The site's designated single-session PCDT Technique (A or B)** should be used if the caudal-most extent of the thrombus is more than 3 cm above the caudal end of the popliteal vein (i.e. tibial vein confluence) and the IVC is not involved, as seen on the initial venogram.

2. **Infusion-First PCDT (Technique C)** should be used if the thrombus extends below the popliteal vein (i.e. into a tibial vein) or into the IVC, as seen on the initial venogram.

3. **The endovascular physician may choose** to use either single-session PCDT or infusion-first PCDT for all other situations (e.g. if the caudal end of the thrombus is within the lower popliteal vein). However, attention should be paid to ensuring that popliteal vein inflow is adequately restored, and the choice of access vein should reflect the needed sheath size.

Safe Venous Access

4. The physician should carefully examine the popliteal fossa with ultrasound prior to access site selection. The popliteal vein may course posterior or posteromedial to the artery. The presence of any popliteal artery branches in the area to be traversed should be actively sought, since inadvertent puncture can lead to significant bleeding in rt-PA recipients.

5. All attempts to obtain venous access must be performed with realtime US guidance.

6. To minimize venous trauma from unsuccessful venipunctures, a small needle and catheter set (e.g. a micropuncture set with 21 gauge needle) should be used to obtain access.

7. If there is any doubt as to the exact vessel entered with the needle, place the inner 3 French catheter of the micropuncture set to inject contrast and confirm entry into the desired vein. If in the artery, remove the catheter and apply manual pressure until hemostasis is obtained.

Venographic Technique

8. Venograms should be performed by hand injection. The only situations in which automated injection is permitted are when a) the IVC must be evaluated for IVC filter placement; b) an initial hand-injection shows that the IVC is not densely thrombosed; and c) hand-injection is

insufficient to opacify the IVC or identify the renal veins to permit safe IVC filter placement.

9. Contrast injections should be adequate to opacify all venous segments from wall to wall, and venograms should be of sufficient quality to distinguish venous inflow from thrombus. The use of undiluted contrast may over-opacify the veins and render an assessment of the clot difficult. Consider using dilute contrast (1:1 or 2:1 contrast to NS ratio) for the venograms.

10. The use of a radiopaque measuring tape is encouraged to assess the thrombus length.

11. For the initial (pre-PCDT) and completion (post-PCDT) venograms, the entire proximal venous system from popliteal vein through infrarenal IVC should be imaged with adequate overlap of segments ($\geq$ 2 cm), even if this requires re-advancing a catheter.

Trellis PCDT (Technique A)

12. When using the Trellis, an 8 French vascular sheath is placed.

13. If there is a stenosis in the common iliac vein (e.g. May-Thurner Syndrome lesion), the cephalad balloon of the Trellis may be inflated in the common iliac vein just below it. It is important to ensure that the balloons are not inflated beyond the radiopaque markers.

14. Examples of rt-PA Dose Allocation for Trellis delivery:

    a. Patient A has 15 cm length of vein thrombosed, and the endovascular physician elects to use 1 mg rt-PA per 3 cm thrombus. He/she will need 5 mg rt-PA (15 divided by 3). The calculated 5 mg of rt-PA, which was originally reconstituted in 5 ml Sterile Water, is diluted to a total volume of 10 ml using NS, and administered via the Trellis.

    b. Patient B has 48 cm length of vein thrombosed, and the endovascular physician prefers to use 1 mg rt-PA per 4 cm thrombus. He/she will need 12 mg rt-PA (48 divided by 4). Since two overlapping segments using the 30-cm Trellis will be required, the calculated 12 mg is divided evenly into two 6-mg aliquots. Each 6-mg aliquot (which was originally reconstituted in 6 ml Sterile Water for a concentration of 1 mg/ml) is separately diluted to 10 ml using NS, and is given into each of the two segments during the two Trellis runs.

15. After oscillation of the Dispersion Wire, decisions as to whether or not to aspirate the rt-PA are generally made in clinical practice by balancing treatment efficacy against the patient's risk of bleeding. As patients who are at higher expected risk of bleeding will largely be excluded from ATTRACT, aspiration of the rt-PA is not recommended for most patients.

16. Dose Limits: 25 mg rt-PA for the initial procedure, 35 mg for all procedures together. After the initial PCDT procedure, the maximum allowed duration of infusion CDT is 24 hours.

17. For Technique A (Trellis) patients, if additional rt-PA is given to treat residual thrombus after initial PCDT (during the initial procedure or at follow-up procedures), it may be delivered via the Trellis, a standard sheath or catheter, or a multisidehole catheter. It may not be given via the AngioJet device. However, the AngioJet may be used to aspirate residual thrombus.

18. Whenever possible, physicians should try to complete PCDT in a single procedure session in Technique A patients. Before resorting to infusion CDT, the adjunctive procedures listed in Protocol Section 7.3.5 should be used. However, clot removal should not be sacrificed, so infusion CDT is recommended if there is substantial residual occlusive thrombus after their use. For Technique A, up to 24 hours of infusion CDT may be given after initial PCDT.

AngioJet PCDT (Technique B, either PowerPulse or Rapid Lysis)

19. When using the AngioJet, a 6 French sheath is often used. Alternately, an 8 French sheath may be placed to accommodate an 8 French guiding catheter (recommended). Either a DVX or a Solent Proxi Catheter may be used.

20. Examples of rt-PA Dose Allocation for AngioJet delivery:

    a. PowerPulse Method: Patient A has 30 cm length of vein thrombosed, and the endovascular physician prefers to use 1 mg rt-PA per 3 cm thrombus. He/she will need 10 mg rt-PA (30 divided by 3). The calculated 10 mg, which was originally reconstituted in 10 ml Sterile Water, is diluted to a total volume of 50 ml using NS. The AngioJet Drive Unit is set to "PowerPulse". The rt-PA solution is pulsed into the clot via foot pedal activation once every 3 seconds during slow Catheter withdrawal through the clot.

    b. Rapid Lysis Method: Patient B has 40 cm length of vein thrombosed, and the

endovascular physician prefers to use 1 mg rt-PA per 4 cm thrombus. He/she will need 10 mg rt-PA (40 divided by 4). The calculated 10 mg, which was originally reconstituted in 10 ml Sterile Water, is diluted to a total volume of 250 ml using NS. The AngioJet Drive Unit is set to "Aspiration". Using the rt-PA solution as infusate, the DVX Catheter is activated by foot pedal during slow withdrawal and advancement of the Catheter in conjunction with a hockey-stick shaped guiding catheter through the thrombus.

21. Dose Limits: 25 mg rt-PA for the initial procedure, 35 mg for all procedures together. After the initial PCDT procedure, the maximum allowed duration of infusion CDT is 24 hours.

22. For Technique B (AngioJet) patients, if additional rt-PA is given to treat residual thrombus after initial PCDT (during the initial procedure or at follow-up procedures), it may be given via the AngioJet, a standard sheath or catheter, or a multisidehole catheter. It may not be given via the Trellis device. The AngioJet may also be used to aspirate residual thrombus.

23. Whenever possible, physicians should try to complete PCDT in a single procedure session in Technique B patients. Before resorting to infusion CDT, the adjunctive procedures listed in Protocol Section 7.3.5 should be used. However, clot removal should not be sacrificed, so infusion CDT is recommended if there is substantial residual occlusive thrombus after their use. For Technique B, up to 24 hours of infusion CDT may be given after initial PCDT.

Infusion-First PCDT (Technique C)

24. When using Infusion-First PCDT, a 6 French sheath may be used.

25. Examples of rt-PA Dose Allocation for infusion CDT:

    a. Normal Weight: Patient A weighs 75 kg, and needs a rt-PA infusion. The proper dose is 0.75 mg/hr (75 kg times 0.01 mg/kg/hr). 10 mg of rt-PA, originally reconstituted in 10 ml Sterile Water, is diluted to a total volume of 1000 ml using NS (which comes to 0.01 mg/ml), and is infused at 75 ml/hr through a multisidehole catheter (= 0.75 mg/hr).

    b. Heavy Patient: Patient B weighs 120 kg, and needs rt-PA infusion. The dose calculates to 1.20 mg/hr (120 kg times 0.01 mg/kg/hr), but the allowed maximum is 1.0 mg/hr. Therefore, 10 mg of rt-PA, reconstituted in 10 ml Sterile Water, is diluted to a volume of

1000 ml using NS (which comes to 0.01 mg/ml), and is infused at 100 ml/hr.

26. Dose Limits: 35 mg overall, given over 30 hours maximum infusion duration. This may include additional bolus doses given during follow-up sessions, per protocol Section 7.3.5.

27. For Technique C (Infusion-First) patients, if additional rt-PA is given to remove residual clot after initial PCDT, it may be delivered via a standard sheath or catheter or a multisidehole catheter. It may not be delivered via the Trellis or AngioJet devices. However, rheolytic thrombectomy with the AngioJet may be used to aspirate residual thrombus.

Treatment of Obstructive Lesions

28. Stenoses and occlusions of the iliac vein and IVC rarely exhibit a durable response to balloon angioplasty alone. Therefore, the investigator is encouraged to apply a low threshold for stent placement when such lesions are encountered. Correction of lesions associated with ≥ 50% venous diameter narrowing, robust filling of collaterals, and/or a measured mean pressure gradient exceeding 2 mmHg is strongly encouraged. Appropriate stent diameters are usually 12-14 mm for the common iliac vein, and 10-12 mm for the external iliac vein and common femoral vein. Note: Physiological narrowing can be seen in the external iliac vein with prone positioning, especially if the bladder is not empty.

29. Balloon angioplasty alone is preferred for lesions below the saphenofemoral junction.

Procedure Completion

30. The procedure is complete when either a) > 90% thrombus removal has been achieved and there is good anterograde venous flow with no residual venous obstructive lesions; b) > 90% thrombus removal was not achieved but the limits of rt-PA dose or infusion duration were reached and use of all adjunctive measures (protocol Section 7.3.5) has been exhausted; or c) a complication or safety issue necessitating discontinuation of therapy has occurred.

31. When the vascular sheath is removed, hemostasis must be achieved by local compression. The use of percutaneous vascular closure devices is not permitted.

7.3 Summary of Forms Documenting DVT Treatment

This Table below summarizes the Case Report Forms that document the study treatments:

CASE REPORT FORMS FOR DVT TREATMENTS

Form	Patients	Items Documented
Initial Anticoagulation Therapy	Both Arms	Pre-randomization initial anticoagulation Post-randomization initial anticoagulation
Initial PCDT	Experimental Arm Only	Details of initial PCDT Anticoagulation used during PCDT Peri-procedural IVC filter
Anticoagulation Status Change	Both Arms	Stop, change, or re-start anticoagulation
Late Endovascular Procedure	Both Arms	Place or retrieve IVC filter PCDT (except for initial use) Iliac vein stenting (late) Saphenous ablation (late)
Follow-Up	Both Arms	Cessation of heparin therapy Warfarin – compliance (INRs) Compression therapy – compliance

7.4 Completion of the Initial PCDT Therapy Form

Upon study start-up, each endovascular physician who has been certified by the Interventions Committee, will be assigned a Treating Endovascular Physician Identification Number. This number should be entered in Item 2 of the introductory section of the Initial PCDT Therapy Form. In Section D of the Initial PCDT Therapy form, the PCDT procedure components are entered. To simplify recording of the essential elements of these procedures, the coordinator should enter each procedure element without excessive concern about the sequence of events. To perform the visual estimation of spontaneous venous flow after PCDT completion that is referred to in Items 3 and 4 in Section F of the Initial PCDT Therapy Form, the physician can briefly “puff” inject 5-7 ml of contrast and observe its dissipation without applying continuous pressure to the syringe (which may artificially simulate the appearance of flow in the vein).

7.5 Elastic Compression Stockings – Ordering Process

Each site will be provided with a training CD and Opaque and JOBST For Men garments in a variety of sizes. When a pair is dispensed (at the 10-day and 6, 12, and 18-month visits), a replacement pair is obtained by e-mailing an order form to BSN Customer Service at attracttrial@bsnmedical.com. Product will be shipped directly to the site.

8 FOLLOW-UP VISITS & OUTCOME ASSESSMENTS

8.1 Overview of Scheduled Visits

Follow-up assessments are required for every randomized patient, even if he/she does not adhere to the protocol-prescribed intervention. Scheduled follow-up clinic visits will occur at 10 days, 30 days, and 6, 12, 18, and 24 months after randomization. Follow-up visits should occur as close as possible to the scheduled dates, per the parameters outlined in Protocol Section 11.

Each Scheduled Follow-up Assessment will include the following elements:

- Administration of Villalta PTS Scale (subject and blinded clinician components, both legs)
- Subject completion of QOL Questionnaire (except Day 10)
- Review of employment history status (except Day 10)
- Review of compression stockings use (except Day 10)
- Review of anticoagulant therapy and current medication
- Recording of INRs collected since last study assessment
- Review of medical care resource utilization, including Cost Diary (MOP Section 10.5)
- Outcome event assessments (below)
- Completion of Follow-Up Form

Outcome event assessments include investigation and/or documentation of:

- Signs or symptoms suggestive of DVT or PE
- Signs or symptoms suggestive of bleeding
- Invasive procedures related to DVT treatment
- Hospitalizations
- Adverse events
- Death

10-day Follow-Up Assessment:

In addition to the elements above, the following will also be done at the 10-day follow-up visit:

- Completion of Leg Pain Severity Form for each leg (subject)
- Measurement of leg circumference (both legs)
- Provision of fitted elastic compression stockings.
- Re-assessment for removal of retrievable IVC filter (if present)
- Platelet count

30-day Follow-Up Assessment

In addition to the elements above, the following will also be done at the 30-day follow-up visit:

- Completion of Leg Pain Severity Form for each leg (subject)
- Measurement of leg circumference (both legs)
- Re-assessment for removal of retrievable IVC filter (if present)
- Bilateral lower extremity Duplex ultrasound exam to assess thrombus extent

6, 12, 18 and 24-Month Follow-Up Assessments:

In addition to the elements above, the following will also be done every 6 months:

- Revised CEAP Classification (both legs)
- Venous Clinical Severity Score (VCSS) (both legs)
- Provision of a new pair of elastic compression stockings
- Collect the Cost Diary and provide the patient with a new one (except the 24-month visit)
- At the 12-month follow-up visit (only), subjects who take part in the Ultrasound Substudy (only) will have a bilateral lower extremity Duplex ultrasound exam to assess for reflux

8.2 Unscheduled Visits

Unscheduled patient visits are expected to occur during follow-up, most commonly to evaluate suspected outcome events. In such instances: a) an unscheduled event visit should be created; b) a complete follow-up assessment should performed as outlined in MOP Sections 8.1 and 8.9 and Protocol Section 9; and c) the assessment should be documented on a Follow-Up Form and on any supplementary forms as outlined in MOP Section 8.4. If a patient in either treatment arm has a compelling clinical need for an unplanned or off-protocol endovascular intervention, he/she should undergo a clinical follow-up assessment (MOP Section 8.4) before treatment, if possible.

8.3 Case Report Forms for Scheduled Visits

For all scheduled visits, the research coordinator should organize the needed case report forms (CRFs) into a "Patient Package" (forms and questionnaires that the subject will be asked to complete) and a "Blinded Clinician Package" (forms that a blinded clinician will complete). The specific components of these two CRF packages are presented below for each scheduled visit:

CRF PACKAGES FOR SCHEDULED FOLLOW-UP VISITS

Visit	Time	Patient Package	Blinded Clinician Package
1	10 days	Leg Pain Severity CRF	Follow-Up CRF
		Villalta PTS Symptoms (Subject) CRF	Villalta PTS Signs (Blinded Clinician) CRF
2	30 days	Leg Pain Severity CRF	Follow-Up CRF
		Villalta PTS Symptoms (Subject) CRF	Villalta PTS Signs (Blinded Clinician) CRF
		Quality of Life Questionnaire	Compression Ultrasound CRF
3	6 months	Villalta PTS Symptoms (Subject) CRF	Follow-Up CRF
		Quality of Life Questionnaire	Villalta PTS Signs (Blinded Clinician) CRF
			Revised CEAP Classification CRF
			Venous Clinical Severity Score CRF
4	12 months	Villalta PTS Symptoms (Subject) CRF	Follow-Up CRF
		Quality of Life Questionnaire	Villalta PTS Signs (Blinded Clinician) CRF
			Revised CEAP Classification CRF
			Venous Clinical Severity Score CRF
			Compression Ultrasound CRF*
5	18 months	Villalta PTS Symptoms (Subject) CRF	Follow-Up CRF
		Quality of Life Questionnaire	Villalta PTS Signs (Blinded Clinician) CRF
			Revised CEAP Classification CRF
			Venous Clinical Severity Score CRF
6	24 months	Villalta PTS Symptoms (Subject) CRF	Follow-Up CRF
		Quality of Life Questionnaire	Villalta PTS Signs (Blinded Clinician) CRF
			Revised CEAP Classification CRF
			Venous Clinical Severity Score CRF
			End of Study CRF

* Note: the 12-month Compression Ultrasound CRF is only needed for Ultrasound Substudy patients.

8.4 Completion of Supplementary Case Report Forms

At both scheduled and unscheduled visits, additional CRFs may need to be completed to document changes in patient status during follow-up. The Table below lists these additional CRFs that may need completion, and the clinical scenarios in which they must be completed:

SUPPLEMENTARY CASE REPORT FORMS

FORM	CLINICAL SCENARIO
Adverse Event	Non-serious Adverse Event occurs within 30 days
	Serious Adverse Event occurs within 24 months
Anticoagulation Change	AC is stopped, changed, or re-started
Compression Ultrasound	Patient has US exam to evaluate for DVT or PE
Death	Patient dies for any reason
End of Study	Patient dies or elects to withdraw from the study early
Late Endovascular Procedure	Patient undergoes IVC filter placement or retrieval
	PCDT Arm patient has repeat PCDT procedure
	Control Arm patient undergoes any PCDT procedure
	Patient has endovascular intervention for venous disease
Serious Adverse Event	Serious Adverse Event occurs within 24 months
Subsequent Hospitalization	Patient is hospitalized or attends emergency room
Suspected Bleeding	Patient experiences bleeding complication
	Patient is evaluated for suspected bleeding
Suspected Venous Thromboembolic Event	Patient experiences DVT or PE during follow-up
	Patient is evaluated for suspected DVT or PE
<u>Clinical Assessment for PTS/QOL:</u> Villalta PTS Symptoms (Subject) Villalta PTS Signs (Blinded Clinician) Quality of Life Questionnaire (Subject)	Patient undergoes unplanned endovascular intervention during follow-up, except for PCDT Arm patients who are being re-treated within 3 months after randomization

8.5 Visit Procedures

The day before follow-up visits, the subject should receive a telephone reminder to not wear compression stockings on the day of the visit, and to not reveal to clinic staff which treatment he/she received (PCDT or no PCDT) and which leg was affected with the DVT. Subjects should ideally be examined in the afternoon to allow the symptoms and signs of PTS to manifest. The day before the visit, study staff should print hardcopies of the relevant CRFs from the ATTRACT website and assemble them into a **Patient Package** and a **Blinded Clinician Package**.

With the patient in the waiting room, a study staff member should approach the patient and:

1. Determine if the patient will have any difficulty filling in the forms (a blinded "helper" or "translator" may be used, and Spanish-translated CRFs may be selected for use).
2. Explain what will take place during the visit;
3. Remind the patient not to reveal which treatment he/she received (PCDT or no PCDT);
4. Complete the cover page of each CRF;
5. Hand the patient the **Patient Package** for that visit (provide a quiet area, a pen, and a tabletop or clipboard), describe its contents, and ask the patient to complete all forms in the Package: 5 brief questions on symptoms for each leg (Villalta PTS Symptoms); a 15-20 minute questionnaire on health, well-being, and leg problems (Quality of Life Questionnaire entitled "Your Health and Well-Being", all visits except for the 10-day visit); and (for the 10-day and 30-day follow-up visits only) a question about his/her leg pain (Leg Pain Severity).
6. Draw the patient's attention to the page with instructions, and respond to any questions; and
7. For the Leg Pain Severity Question, ask the patient to respond for each leg, by circling the appropriate number on the 7-point scale on the two forms supplied.
8. The patient should complete the above measures after the staff member leaves the area**.**

Next, in a well-lit examination room, a **blinded clinician** (nurse or physician) should:

1. Remind the patient not to reveal what treatment he/she received (PCDT or no PCDT), or how he/she responded to the questionnaire and CRFs, to the examining clinician. The examining clinician must be blinded to treatment allocation and patient responses;
2. Make sure the legs are unclothed and the patient is sitting facing the examining clinician;
3. Evaluate and record the Villalta PTS Signs for each leg (see MOP Section 8.6);
4. Measure and record the leg circumference for each leg (see MOP Section 8.6);
5. Assess and record the Revised CEAP Clinical Class for each leg (see MOP Section 8.7);
6. Assess the patient using the VCSS measure for each leg, and record (MOP Section 8.8);

7. Review the patient-completed Villalta PTS Symptoms CRF, Quality of Life Questionnaire, and Leg Pain Severity CRF for completeness. If anything is missing, the blinded clinician should politely (without coercion) ask the patient if he/she would like to complete the form. This is particularly important for the Villalta PTS Symptoms CRF.

Use of Follow-up Ultrasound Exam Information:

At the 1-month follow-up visit for all patients, and at the 12-month follow-up visit for patients in the Ultrasound Substudy (only), an ultrasound exam is performed after the completion of the above-described clinical outcome assessments. Before performing the ultrasound exam, the research team should make a clinical determination as to whether the patient has had recent symptoms or signs that should prompt investigation for suspected recurrent VTE. If yes, then follow the procedures to evaluate a suspected recurrent VTE event (MOP Section 8.9). In this situation, the investigator is permitted to use the ultrasound exam information along with the clinical findings to modify the patient's DVT treatment if he/she believes that this is indicated. However, if the patient was not clinically suspected to have recurrent VTE prior to performance of the ultrasound exam, then its findings should not be used to modify the treatment approach.

After the visit and definitely before the end of his/her shift, study staff should:

1. Enter the patient responses for the Villalta PTS Symptoms and Leg Pain Severity (if applicable) measures, and the blinded clinician responses for the Villalta PTS Signs (including leg circumference information), the Revised CEAP, and VCSS forms into ORCCID;
2. Make a copy of the Villalta PTS CRFs (both Symptoms and Signs), the Leg Pain Severity CRF, QOL Questionnaire, Compression Ultrasound CRF (if applicable), Cost Diary, and other CRFs that were used, making sure that the CRFs are correctly identified with the Subject ID Number, Clinical Center Number, dates, and sign-off, as required;
3. Place the original copies of the CRFs and cost diary into a labeled envelope and send by courier to the DCC. Please retain the copies in the Patient Binder at the Clinical Center. When the mailed forms are received at the DCC, staff will enter the QOL data into ORCCID;
4. The CRFs should be batch-shipped to the DCC on a monthly basis, along with de-identified source documents and venogram images (PCDT patients only) (see MOP Section 10).
5. For Ultrasound Substudy patients, the Compression Ultrasound CRF and exam images documenting the 1-year exam should be de-identified and submitted directly to VasCore. A separate Ultrasound Substudy Manual will be provided to Substudy Clinical Centers.
6. See **MOP Appendix B** for a concise summary of the logistics of data submission.

8.6 Instructions for Completion of the Villalta PTS Assessment

The Villalta PTS assessment has two components, a **subject component** that is self-completed by the patient to record PTS Symptoms (subject CRF is in the **Patient Package**), and a **blinded clinician component** that is completed by a blinded clinician during exam of the patient's legs to document PTS Signs (clinician CRF is in the **Blinded Clinician Package**).

1. First, the subject completes the Villalta PTS Symptoms (Subject) Form for the right leg. The subject is asked "In general, how would you rate the following symptoms in your **RIGHT** leg? (please check one response for each symptom)". The 5 symptoms to be rated by the subject (check box options: No or Minimal, Mild, Moderate, Severe) are
   a. Cramps
   b. Itching
   c. Pins and needles
   d. Leg heaviness
   e. Pain

2. Next, the subject repeats the same procedure and completes the Villalta PTS Symptoms (Subject) Form, as above, for the **LEFT** leg.

3. Next, a clinician who is blinded to the subject's responses on the Villalta PTS Symptoms (Subject) Form and to the patient's treatment allocation examines the subject and rates the following 6 signs on the Villalta PTS Signs (Blinded Clinician) Form by checking one response for each sign (check box options: No or Minimal, Mild, Moderate, Severe) (for guidance, see the graphic Visual Aid that was provided to each site) for the **RIGHT** leg:
   a. Pretibial edema
   b. Skin induration
   c. Hyperpigmentation
   d. Venous ectasia
   e. Redness
   f. Pain during calf compression

4. For the **RIGHT** leg, the blinded clinician answers the question "Is an ulcer present" (No/Yes), measures the calf circumference using a tape measure (measured 10 cm below the tibial tuberosity), and records both responses on the Villalta PTS Signs (Blinded Clinician) Form.

5. Next, the blinded clinician repeats the steps in Items 3 and 4 above for the **LEFT** leg, and records the information on the Villalta PTS Signs (Blinded Clinician) Form.

Note: For a refresher on the performance of the Villalta PTS assessment, see the PowerPoint presentation on use of the Villalta PTS Scale on the ATTRACT website (www.attract.wustl.edu).

8.7 Instructions for Completion of the Revised CEAP Classification Form

On the revised CEAP Classification Form, the blinded clinician is asked: "For both legs, please check one box (i.e. Present vs. Absent) for each finding". There are 7 findings to be assessed (please see PowerPoint presentation on CEAP Classification System at www.attract.wustl.edu).

1. Telangiectasias (spider veins) or reticular veins
2. Varicose veins
3. Edema
4. Skin changes: pigmentation or venous eczema
5. Skin changes: lipodermatosclerosis
6. Healed venous ulcer
7. Active venous ulcer

If all findings on both legs are checked as "absent", the blinded clinician is asked to check the box to confirm: "There are no visible or palpable signs of venous disease in either leg".

8.8 Instructions for Completion of the Venous Clinical Severity Score (VCSS) Form

On the VCSS Form, the blinded clinician is asked: ""Complete the following form for both legs. Please check one box for each item." Please see the PowerPoint presentation on the VCSS measure at www.attract.wustl.edu. Please use the guidelines below to score the nine items:

Pain or other discomfort (i.e., aching, heaviness, fatigue, soreness, burning)
The blinded clinician describes the four categories of leg pain or discomfort that are outlined below to the patient and asks the patient to choose, separately for each leg, the category that best describes the pain or discomfort the patient experiences.

Absent = 0	None
Mild= 1	Occasional pain or discomfort that does not restrict regular daily activity
Moderate = 2	Daily pain or discomfort that interferes with, but does not prevent regular daily activities
Severe = 3	Daily pain or discomfort that limits most regular daily activities

Varicose Veins

The blinded clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's superficial veins. Note: Veins must be ≥ 3 mm diameter to qualify as "varicose veins".

Absent = 0	None
Mild = 1	Few, scattered, varicosities that are confined to branch veins or clusters, including "ankle flare" or "corona phlebectatica", defined as greater than 5 blue telangiectasias at the inner or sometimes the outer edge of the foot.
Moderate = 2	Multiple varicosities that are confined to the calf or the thigh
Severe = 3	Multiple varicosities that involve both the calf and the thigh

Venous Edema

The blinded clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's pattern of leg edema. The examination may be supplemented by asking the patient about the extent of leg edema that is experienced.

Absent = 0	None
Mild = 1	Edema that is limited to the foot and ankle
Moderate = 2	Edema that extends above the ankle but below the knee
Severe = 3	Edema that extends to the knee or above

Skin Pigmentation

The blinded clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's skin pigmentation. Pigmentation refers to color changes of venous origin and not secondary to other chronic diseases.

Absent = 0	None, or focal pigmentation confined to the skin over varicose veins
Mild = 1	Pigmentation that is limited to the perimalleolar area
Moderate = 2	Diffuse pigmentation that involves the lower third of the calf
Severe = 3	Diffuse pigmentation that involves more than the lower third of the calf

Inflammation

The blinded clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's skin inflammation. Inflammation refers to erythema, cellulitis, venous eczema, or dermatitis, rather than just recent pigmentation.

Absent = 0	None
Mild = 1	Inflammation that is limited to the perimalleolar area
Moderate = 2	Inflammation that involves the lower third of the calf
Severe = 3	Inflammation that involves more than the lower third of the calf

Induration

The blinded clinician examines the patient's legs and, for each leg, chooses the category that best describes the patient's skin induration. Induration refers to skin and subcutaneous changes such as chronic edema with fibrosis, white atrophy and lipodermatosclerosis.

Absent = 0	None
Mild = 1	Inflammation that is limited to the perimalleolar area
Moderate = 2	Inflammation that involves the lower third of the calf
Severe = 3	Inflammation that involves more than the lower third of the calf

Number of Active Ulcers

The blinded clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the number of active ulcers.

Absent = 0	None
Mild = 1	One ulcer
Moderate = 2	Two ulcers
Severe = 3	Three or more ulcers

Active Ulcers: Duration

If there is at least one active ulcer, the blinded clinician describes the four categories of ulcer duration that are outlined below to the patient and asks the patient to choose, separately for each leg, the category that best describes the duration of the longest unhealed ulcer.

Absent = 0	No active ulcers
Mild = 1	Ulceration present for less than 3 months
Moderate = 2	Ulceration present for 3 to 12 months
Severe = 3	Ulceration present for more than 12 months

Active Ulcers: Size

If there is at least one active ulcer, the blinded clinician examines the patient's legs, and for each leg, chooses the category that best describes the size of the largest active ulcer.

Absent = 0	No active ulcer
Mild = 1	Ulcer of less than 2 cm diameter
Moderate = 2	Ulcer of 2 to 6 cm diameter
Severe = 3	Ulcer of greater than 6 cm diameter

8.9 Documentation of Suspected Safety Outcome Events

See Protocol Section 9 for a description of the standardized sequence of clinical investigation for suspected safety outcome events and the criteria for interpretation of test results that will be applied by the Independent Central Adjudication Committee. In this section, the requirements for documenting suspected safety outcome events and their clinical evaluation are outlined.

Documentation of Suspected (Symptomatic Recurrent) DVT:

A Suspected Venous Thromboembolic Event CRF becomes due when site personnel become aware of a patient having a suspected symptomatic recurrent DVT (Protocol Section 9.3). An Adverse Event CRF should also be completed if: a) the event occurs ≤ 30 days after randomization; b) the event occurs ≤ 30 days after a subsequent use of the Study Drug (rt-PA); **or** c) the event meets criteria for a serious adverse event (SAE) (in which case a Serious Adverse Event CRF should also be completed and the CCC should be notified). The CRF(s)

are submitted via ORCCID. The **de-identified** support documents below should be sent by courier to the DCC with a Suspected Symptomatic DVT Adjudication Event Transmittal Form and using ATTRACT Trial mailing labels (both available at www.attract.wustl.edu):

- D-Dimer report, if performed
- The report and images documenting the most recent "previous" lower extremity Duplex ultrasound exam in the same leg (i.e. obtained prior to the current suspected DVT event)
- Initial Compression Ultrasound report and CRF and images, if performed (i.e. that documents the initial US exam used to evaluate the current suspected DVT event)
- Serial Compression Ultrasound report and form and images, if performed (i.e. that documents a subsequent US exam used to evaluate the current suspected DVT event)
- Venogram report and images, if performed
- CT Venogram report and images, if performed
- Clinic Notes relating to the suspected DVT event
- INR report, if performed

Documentation of Suspected (Symptomatic) Pulmonary Embolism:

A Suspected Venous Thromboembolic Event CRF becomes due when site personnel become aware of a patient having a suspected symptomatic PE (see Protocol Section 9.2). An Adverse Event CRF should also be completed if: a) the event occurs ≤ 30 days after randomization; b) the event occurs ≤ 30 days after any subsequent use of the Study Drug (rt-PA); **or** c) the event meets criteria for a serious adverse event (SAE) (within 24 months after randomization; a Serious Adverse Event CRF should also be completed and the CCC should be notified). The CRF(s) are submitted through ORCCID. The **de-identified** support documents below should be sent by courier to the DCC with a Suspected Symptomatic PE Adjudication Event Transmittal Form and using ATTRACT Trial mailing labels (both available at www.attract.wustl.edu):

- D-Dimer report, if performed
- Ventilation/Perfusion Lung Scan report and images, if performed
- Spiral CT Scan report and images, if performed
- Pulmonary Angiography report and images, if performed
- The report and images documenting the most recent previous lower extremity Duplex ultrasound exam in the same leg (i.e. obtained prior to the current suspected PE event), if the presence of acute DVT is being used to diagnose acute PE

- Initial Compression Ultrasound report and CRF and images, if performed (i.e. that documents the initial US exam used to evaluate the current suspected DVT event), if the presence of acute DVT is being used to diagnose acute PE
- Serial Compression Ultrasound report and form and images, if performed (i.e. that documents a subsequent US exam used to evaluate the current suspected DVT event), if the presence of acute DVT is being used to diagnose acute PE
- Chest X-Ray report, if performed
- Clinic Notes relating to the suspected PE event
- INR report, if performed

Documentation of Suspected Bleeding:

A Suspected Bleeding CRF becomes due when site personnel become aware of a study patient having suspected bleeding (see Protocol Section 9.1). An Adverse Event CRF should also be completed if: a) the event occurs ≤ 30 days after randomization; b) the event occurs ≤ 30 days after any subsequent use of the Study Drug (rt-PA); **or** c) the event meets criteria for a serious adverse event (SAE) (within 24 months after randomization; a Serious Adverse Event CRF should also be completed and the CCC should be notified). . The CRF(s) are submitted online through ORCCID. The **de-identified** support documentation below should be sent by courier to the DCC along with a Suspected Bleeding Adjudication Event Transmittal Form and using ATTRACT Trial mailing labels (both available at www.attract.wustl.edu):

- Diagnostic test results, if performed
- Hemoglobin lab reports before, during, and after the bleeding episode, if performed
- Transfusion records, if applicable
- Operative reports, if applicable
- Clinic Notes, or other signed description that summarizes clinical presentation, duration, severity, diagnostic testing, and/or consequences of suspected or confirmed bleeding)
- INR report, if performed

Documentation of Patient Death:

A Death CRF becomes due when site personnel become aware of a study patient's death (see Protocol Section 9.4). A Follow-Up CRF should be completed to document the patient's status from the time of the last follow-up visit to the time of death, and Adverse Event, Serious Adverse Event, and End of Study CRFs must also be submitted. The CRF(s) are submitted via ORCCID. Support documentation should include any of the items below that are available – these **de-**

identified materials should be sent by courier to the DCC with a Death Adjudication Event Transmittal Form and using ATTRACT Trial mailing labels (available at www.attract.wustl.edu):

- Doctor's and nurse's notes in hospital or clinic chart, if applicable
- Hospital discharge summary, if applicable
- Information from subject's physician, if applicable
- Description from family or other contact, if applicable
- Other signed description that summarizes clinical presentation, duration, severity, diagnostic testing, and/or other information relevant to the fatality
- Autopsy Report, if applicable

Supplementary Forms

As outlined in MOP Section 8.4, additional CRFs may need completion if the above suspected or confirmed events fulfill the criteria in Protocol Section 13.1.2 for SAE reporting (Serious Adverse Event CRF), result in hospitalization (Subsequent Hospitalization CRF), and/or cause a change in DVT treatment (Anticoagulation Change CRF or Late Endovascular Procedure CRF),

8.10 Performance and Documentation of Compression Ultrasound Exams

Compression US exams are performed at baseline, at 30-day follow-up, and as needed to evaluate suspected recurrent VTE. The baseline US exam confirms the presence of acute DVT and identifies its location and extent. The 30-day follow-up exam establishes a new baseline (after the initial treatment phase) against which later unscheduled US exams can be compared.

Patient Preparation

- The patient should be NPO for 8-12 hours (for the iliac vein assessment) when possible
- The patient should be supine in reverse Trendelenburg (head elevated about 30 degrees)
- The leg should be externally rotated with the knee flexed slightly; instruct the patient to shift his/her weight to the ipsilateral hip to assist with external rotation of the limb
- Place a pillow underneath/alongside the hip of the leg being examined to maximize comfort, keeping the muscles relaxed.

Vessels Examined

- Iliac veins (when possible)
- Common femoral veins (CFV)

- Profunda femoris vein (PFV)
- Femoral vein (FV)
- Popliteal vein (PV)
- Tibial vein confluence

Exam Conduct and Documentation

Please refer to Appendix 12 of the study Protocol for details on the strongly recommended ultrasound exam technique. Of note, in addition to a complete evaluation of the proximal veins in the ipsilateral leg, always perform Doppler interrogation of the contralateral CFV, with gray-scale compression, color, and Doppler imaging, and compare the results to the ipsilateral CFV.

Completion of the Compression Ultrasound CRF

1. For best comprehension, please refer to **MOP Appendix M**, which contains an example of a properly completed Compression Ultrasound CRF, while reading the instructions below.
2. For purposes of the ATTRACT Trial, "full compressibility" refers to complete apposition of the vein walls during the external application of ultrasound probe pressure.
3. The presence or absence of full compressibility of the CFV, FV, and PV is first recorded by checking the respective "Yes" or "No" boxes on the Compression Ultrasound CRF.
4. If "No" is checked for the CFV, the anteroposterior diameter of the vein at the inguinal ligament should be measured during compression and recorded in millimeters in the adjacent "Residual diameter" boxes on the Compression Ultrasound CRF. This distance is measured from a freeze frame B-mode image – the sonographer places digital calipers on the anterior and posterior vein walls, and the ultrasound machine measures the vein.
5. If "No" is checked for the PV, the anteroposterior diameter of the vein in the middle of the popliteal fossa should be measured during compression and recorded in millimeters in the adjacent "Residual diameter" boxes on the Compression Ultrasound CRF, as in #2 above.
6. The point of transition from fully compressible to not fully compressible indicates a thrombus margin (i.e. the "end of a clot"). The position of the upper and lower thrombus margins (if visible) should be marked on the subject's skin to facilitate subsequent measurements.
7. The presence and extent of thrombus in the deep veins should be marked (drawn or shaded) on the diagram on the Compression Ultrasound CRF (see example below).
8. The distance of each thrombus margin from either the saphenofemoral junction or the calf vein trifurcation (known as "venous reference points") should be measured with a tape measure. These distances should be written on the Compression Ultrasound CRF (there is

no prepared box for this), making sure that the venous reference point for each measurement is clear. Placing hand-drawn brackets around the two points that define the measurement (i.e. the thrombus margin and the venous reference point) is suggested.

Labeling of Ultrasound Images

DICOM images are the preferred format for image submission. Label the US images as follows:

- Gray scale – Label images by anatomic location and by compression
- Spectral Doppler – Label by anatomic location and phase (respiratory, valsalva, or augmentation). In the presence of occlusive thrombus, document absence of flow.
- Residual vein diameter measurements – Document images displaying the size of the compressed vein at the CFV, PV, and any site that does not fully compress.

8.11 Subject Reimbursement for Follow-Up Visits

The study team should thank the patient for attending his/her follow-up visit and arrange to have his/her time and travel expenses compensated (per study Protocol Section 18.6.2, subjects should receive $20 per visit starting at the 1-month follow-up visit) in a timely fashion.

8.12 Study Exit Procedures

Patients will exit the study in one of several circumstances:

1) The subject completes 24 months of follow-up as planned. In this instance, an End of Study Form is completed and submitted via ORCCID to the DCC;

2) The subject dies during follow-up (see MOP Section 8.9 for procedures to follow); or

3) The subject elects to withdraw from the study. In general, subjects should be encouraged to remain in the study until follow-up is completed but should be informed that they have the right to withdraw at any time without compromise to their subsequent care. If a subject elects to withdraw prior to completion of follow-up, he/she should be asked for permission:

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

If a subject elects to withdraw and is willing to be contacted by phone (or misses a visit but can be reached by phone within 1 month), the 5 patient-reported symptoms of the Villalta PTS Scale should be queried over the phone. The QOL Questionnaire should also be administered by phone.

9 ADVERSE EVENT REPORTING

9.1 Definition of Adverse Event (AE)

An AE 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.

9.2 Definition of Serious Adverse Event (SAE)

A SAE 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.

9.3 Definition of 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.

9.4 Adverse Event Reporting Requirements and Case Report Form

Information regarding AEs should be solicited at all scheduled and unscheduled follow-up visits. An Adverse Event Form must be completed and submitted electronically to the DCC for every AE that a) occurs within 30 days after randomization; b) occurs within 30 days after subsequent use of the Study Drug (rt-PA); or c) meets the criteria for a Serious Adverse Event (SAE). The date of onset of the AE, the date of resolution (if known), and the date of Adverse Event Form completion should be clearly noted. The event should be categorized by its intensity or severity, expectedness, relatedness to the research study, relatedness to use of the Study Drug (rt-PA), outcome, and treatment or action taken, as described in Section 13.3 of the study protocol. In addition, the AE should be categorized using the Society of Interventional Radiology (SIR) standards for outcome-based reporting of complications. To standardize reporting of AEs per SIR reporting standards, please use the following guidelines:

Minor therapy includes non-invasive interventions which are associated with minimal, if any, patient risk (e.g. hydration, benadryl to treat an allergic reaction, antibiotics to treat cellulitis).

Moderate therapy includes non-invasive interventions that can be associated with significant patient risk (e.g. transfusion of red blood cells).

Major therapy includes invasive procedures (e.g. surgical hematoma evacuation, percutaneous abscess drainage) and other interventions that are associated with substantial patient risk.

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.

9.5 Serious Adverse Event Reporting Requirements and Case Report Form

All SAEs occurring from randomization through 24 months follow-up must be reported. Any SAE occurring after a subject has completed or discontinued study participation should be reported if it was possibly related to rt-PA exposure. If a cancer or congenital anomaly develops in a subsequently conceived offspring of a female subject, this should be reported as a SAE. As Dr. Suresh Vedantham, ATTRACT Principal Investigator, is the IND Holder, all SAEs should be reported to the CCC as described here and in study Protocol Section 13.4:

1. Complete the SAE Form electronically, print the form, sign and date, and e-mail or fax it **within 24 hours of knowledge of the event** (Monday-Friday) to the CCC, along with any relevant medical reports (de-identified to comply with HIPAA regulations), at this address:

   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. Transmit the electronic Serious Adverse Event CRF to the DCC. If the SAE is fatal, follow the expedited procedures described in Protocol Section 13.4 and MOP Section 8.9.

4. As more information becomes available, submit additional SAE Forms to the CCC and DCC.

9.6 CCC Review of SAE Categorization

At the CCC, Dr. Vedantham will review the SAE report and obtain any needed clarifications by telephone and/or e-mail with the Clinical Center investigator(s). The investigator's description and categorization of the SAE per the criteria in Protocol Section 13.3, and any additional relevant information, will then be reviewed at the CCC by the ATTRACT Trial Safety Officer:

James R. Duncan, M.D., Ph.D.
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

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 the use of rt-PA, then the event will be reported as such.

9.7 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.

9.8 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 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 will then be responsible for providing this Report to their IRBs.

9.9 Reporting Requirements for Unanticipated Problems that are not SAE

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.

10 DATA

Data collection in the ATTRACT Trial will be performed via an Electronic Data Capture (EDC) system. The DCC's Online Remote Collection of Clinical Information and Data (ORCCID) system incorporates a clinical database, data query process, and visit completion tracking to ensure that the data submission is complete, timely, accurate, and of high quality. Designated ATTRACT research personnel at the sites will be provided password-protected access to ORCCID. A secure and confidential electronic study database will be maintained by the DCC.

10.1 Case Report Form Instructions

The following general guidelines should be followed for CRF completion:

1. For ease of use, the research coordinator may print off the CRFs needed for each visit and complete the paper forms by hand. The data can then be entered into ORCCID.
2. Read all questions carefully and complete all required areas of the CRF.
3. Follow the on-line instructions for CRF completion and the directions on the CRFs.
4. All questions must be answered. Do not leave questions blank.
5. Only Clinical Center staff who are designated on the Delegation of Authority/Responsibility Form may complete and/or sign off on CRFs.
6. CRFs available on ORCCID should be electronically signed by the site PI or designee, preferably at the visit level.

7. Original paper CRFs should be signed and dated by the site PI or designee, and sent by courier to the DCC. See **MOP Appendix B** for a summary of data submission information.

10.2 Data Clarifications

All entered data will be checked at the DCC for completeness, accuracy, and consistency. If any data are unclear, incomplete, or appear incorrect, a Data Clarification Query (DCQ) will be generated. Each query will be represented by a Clarification Flag next to the data in question in the ORCCID database. A CRF Query Icon will be used to provide a brief explanation of what is missing or needs clarification. When a CRF Query is added, the user will see an icon beside the Subject ID Number in the subject list of the ORCCID database. This is an indication that a DCQ has been issued and requires a response. DCQs are also accessible by clicking on the **View Queries** link on the CRF screen in the **Form Management** section. Please respond immediately to queries as they are received. "Save and Submit" cannot be applied to a CRF until all required corrections have been made and all flags have been cleared. Please refer to the on-line ORCCID Manual (also available for download or print) or the E-Learning system for further information about the processing of queries.

10.3 Source Documentation

Source documents are required to support and verify subject data. The specific source documentation required by the DCC is outlined on the last page of each CRF. Blinded, de-identified source documents that must be identified with the patient's information using the source document labels (available at www.attract.wustl.edu) and sent by courier to the DCC. Source documents include all required original records of observation, results, and activities necessary to reconstruct and evaluate the subject. Source documents include, but are not limited to, laboratory reports, radiographs, ultrasound exam reports and images, radiology reports, patient progress notes, clinic notes, hospital charts, and any other records or reports of procedures performed during the study period.

10.4 DCC Reports to Clinical Centers

The following status reports will be available to Clinical Center personnel on a monthly basis to optimize study and data management.

1. Monthly Trial Status Report detailing overall study enrollment with breakdown by Center. This Report will be posted on the ATTRACT website.

2. CRF Status Reports outlining any overdue assessments and listing any outstanding CRFs not yet received by the DCC from the Clinical Center. These reports will be sent electronically by the DCC to the applicable Clinical Centers.

10.5 Economic Data Collection & Submission to DCC

Economic data will be collected in two ways. First, during the trial, resource utilization data will be collected from patients by the Clinical Center research coordinators, recorded on CRFs, and submitted to the DCC in the usual fashion using the ORCCID system. Soon after randomization, the coordinator should give the patient an ATTRACT Cost Diary and review the instructions within with the patient. The Cost Diary is a memory aid that is intended to help the patient recall medical care and expenses he/she incurred since the last visit. At each follow-up visit, the coordinator should review the Cost Diary with the patient to jog his/her memory of interval medical care and expenses. The Cost Diary is not a primary data collection instrument – the information in the Cost Diary should not just be copied onto the CRFs - rather, it is a tool that helps the coordinator query the patient about his/her interval medical care and expenses, to enable to coordinator to more accurately record this information on the CRFs. At the 6, 12, 18, and 24-month follow-up visits, the Cost Diary should be collected, sent to the DCC, and a new one provided (except at the final visit). The Table below lists CRFs that record economic data:

CASE REPORT FORMS WHICH RECORD ECONOMIC DATA

Form	Patients	Items Documented
Baseline	Both Arms	Employment status
Follow-Up	Both Arms	Employment status, medication use, missed workdays, family care, missed family member workdays, home health visits, visits to emergency rooms and outpatient clinics
Initial PCDT Therapy	PCDT Arm	Endovascular procedure resource use Hospitalization details
Late Endovascular Procedure	Both Arms	Endovascular procedure resource use Hospitalization details

Subsequent Hospitalization	Both Arms	Hospitalization details Procedures performed in hospital

Note: Coordinators should have a low threshold to record re-hospitalizations or procedures that may possibly relate to venous disease or its complications. These events will be adjudicated as to whether or not they are related to venous disease at MAHI according to pre-defined criteria.

Second, UB-04 forms and itemized hospital bills will be collected directly from participating non-VA hospitals by staff from the Health Economic Core Laboratory at St. Luke's Mid-America Heart Institute (MAHI) in Kansas City, MO. Please follow the instructions in the Economic Study Procedures section (**MOP Appendix L**) to incorporate the Economic Study into the ICF, to obtain IRB approval for the Economic Study and Medical Billing Release form, to properly explain the Economic Study and Medical Billing Release form to the patients, to initiate MAHI collection of patient billing data, to review the use, collection, and submission of the Cost Diaries to the DCC, to see a list of answers to commonly-asked questions, and to contact MAHI staff.

10.6 Venogram Submission to the DCC

Patients who are randomized to the PCDT Arm will have pre-PCDT and post-PCDT venograms submitted to the DCC for evaluation. Please follow the following venogram submission process:

1. The endovascular co-investigator should work with the research coordinator and radiology technologist to save the representative images documenting the pre-PCDT and post-PCDT assessments of the proximal veins onto appropriate digital media. The DICOM images should be downloaded at the Clinical Center, de-identified, and then saved on a CD-ROM.

2. Ensure that ATTRACT Trial, Clinical Center Number, and Subject ID Number are embedded onto the CDs. Please DO NOT embed local software used at the Clinical Center onto the CDs. Also, DO NOT place labels directly onto the CDs. Any information written directly onto the CDs should only be done so by using special CD type markers.

3. Each CD-ROM case must be labeled with an ATTRACT-specific label (available at www.attract.wustl.edu) that identifies the ATTRACT Trial, Clinical Center Number, Subject ID Number, date of the venogram, and whether the included images were obtained before

the start of thrombus removal (label as “pre-PCDT”) or after completion of thrombus removal and adjunctive procedures (label as “post-PCDT”). The pre-PCDT and post-PCDT images may be saved on the same CD-ROM only if each set of images is stored in a separate folder named “Pre-PCDT” or “Post-PCDT”. Because PCDT procedures can involve multiple venograms performed at varying timepoints during the treatment process, take extra care not to include images that were obtained at “intermediate” timepoints (i.e. during PCDT).

4. Complete a Venogram Transmittal Form (available at www.attract.wustl.edu), and enclose it with the venograms being sent by courier to the DCC. Retain a copy of this form at the site.

5. Alert the DCC that a shipment is being sent by e-mailing Marc Filion, DCC Study Coordinator (filion@mcmaster.ca). For optimal efficiency, batched shipments of venograms, source documents, paper CRFs, Screening Logs, and other materials may be sent by courier on a monthly basis to the DCC at the following **DCC mailing address**:

ATTRACT Study Coordinator, OCOG
Juravinski Hospital
711 Concession Street, G(60) Wing, 1st Floor
Hamilton, ON L8V 1C3
CANADA

10.7 Compression Ultrasound Retention & Submission to the DCC

Retention of Baseline and 30-Day Compression US Exams

1. When the baseline and 30-day compression US exams are performed, the images should be downloaded at the Clinical Center, de-identified if possible, and then saved onto a CD-ROM. A Compression Ultrasound Form should be completed and submitted to the DCC.

2. Please ensure that ATTRACT Trial, Clinical Center Number, and Subject ID Number are embedded on the CD. Please DO NOT embed local software used at the Clinical Center onto the CDs. Also, DO NOT place labels directly onto the CDs. Any information written directly onto the CDs should only be done so by using special CD type markers

3. Each CD-ROM case must be labeled with an ATTRACT-specific label (available at www.attract.wustl.edu) that identifies the ATTRACT Trial, Clinical Center Number, Subject

ID Number, date of the US exam, and whether it was a baseline, 1-month follow-up, or unscheduled exam.

4. Archive the properly labeled, de-identified US exams for later retrieval if this is needed.

Submission of Unscheduled and Comparison Compression US Exams

1. When an unscheduled compression US exam is performed to evaluate suspected recurrent VTE, download the exam images, de-identify them, save them onto CD-ROM, and label the images and CD-ROM case as described above.

2. Complete a Compression Ultrasound CRF for the new exam and submit it to the DCC.

3. Retrieve the CD-ROM which contains the images of the last previous archived compression US exam in the leg with the suspected recurrent DVT.

4. Complete an Adjudication Event Transmittal Form (available at www.attract.wustl.edu) and send the Form and CD-ROMs containing the new and old exams by courier to the DCC.

10.8 Substudy Ultrasound Submission to VasCore

The sites that are selected to participate in the Ultrasound Substudy will receive a separate Ultrasound Substudy Manual which details the submission of these exams directly to VasCore.

10.9 Independent Central Adjudication Committee

All suspected clinical events and venographic outcomes will be evaluated by an Independent Central Adjudication Committee (ICAC) that is unaware of the patient's treatment allocation. The sequence of investigation by the Clinical Centers and the criteria for interpretation of test results by the ICAC will be standardized as described in the study Protocol and Adjudication Manual. The DCC, acting as Secretariat to the ICAC, will collate the images, reports, and source documentation for submission to the ICAC and will provide the administrative support needed to facilitate adherence to the application of pre-defined adjudication criteria. When appropriate, the DCC will forward Duplex ultrasound images to VasCore to obtain their interpretation. The ICAC will then review the clinical information along with VasCore's interpretation, then adjudicate the event. All adjudication decisions of the ICAC will be final. The final analysis of study outcomes will be performed on adjudicated data.

11 SITE MONITORING

11.1 Site Monitoring Plan

The CCC at Washington University will monitor each Clinical Center to ensure that all study Protocol requirements are being met; that federal, state, and local regulations are being followed; and that best patient safety practices are being followed per the study Protocol. To accomplish this, the Site Monitoring Committee at the CCC will communicate regularly with the DCC to obtain pre-specified site-specific data, and will also periodically query specific data needed to address Clinical Center issues as they arise. The Site Monitoring Committee will also develop a structured plan for routine monitoring of the Clinical Centers. This plan will include evaluation of the following elements of Clinical Center performance, at a minimum:

1. Subject screening and enrollment, including enrollment by gender, race, and ethnicity.
2. Reporting of adverse events.
3. Adherence to limits on rt-PA dosing and endovascular device use.
4. Documentation of rt-PA receipt, storage, use, and destruction.
5. Maintenance of HIPAA compliance
6. Completeness of documentation in Site Regulatory Binder (see **MOP Appendix N**)
7. Completeness of documentation in Patient Binders (see **MOP Appendix O**)
8. Acquisition of informed consent (and child assent for minors) in all study subjects
9. IRB documentation
10. Other issues of protocol adherence

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 CRFs, pursuant to U.S. GCPs and other federal and local regulations. Each Clinical Center and its site PI will permit authorized representatives of the FDA, NHLBI, Washington University, local health authorities, and industry partners to inspect relevant facilities and records.

11.2 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 coordinator 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 result in a letter from the Principal Investigator or Study Chair to the site investigator(s) and research coordinator, informing them of the violation and requesting a written explanation. The ATTRACT research coordinator 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, the site will be dropped as an enrollment center. Review of all protocol violations will be a standard component of the routine CCC team meetings led by Dr. Vedantham. All major protocol violations will also be reviewed by the Operations Committee.

11.3 Site Regulatory Binder

Each Clinical Center must securely maintain a Site Regulatory Binder at the Clinical Center. The required contents of the Site Regulatory Binder are listed in **MOP Appendix N**.

11.4 Patient Binder

A detailed individual Patient Binder should be maintained for each study participant to keep track of his/her involvement in the study. The required contents are listed in **MOP Appendix O**.

11.5 Record Retention

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 ICFs, source documentation for values or responses in the CRFs, supporting documentation for AEs, laboratory test results, and medication inventory records must be retained for at least 2 years after the study ends. The CCC and DCC reserve the right to secure data clarification & additional medical documentation on enrolled trial patients. To avoid error, the site investigator should contact the CCC before destroying any records or reports pertaining to the trial to ensure they are no longer needed.

12 SUBAWARDS & PAYMENT MILESTONES

12.1 Payment Structure

This section summarizes the reimbursements that are provided by the Washington University CCC to the Clinical Centers for work performed on the ATTRACT Trial. This document reflects funding expectations as of January 23, 2011; however, this projected schedule could change if NIH or industry funding levels for the ATTRACT Trial change. The ATTRACT Trial is primarily funded by the NIH, but some of the funding is derived from industry partners. Because NIH dollars must be separately accounted for and are subject to more stringent regulations, separate sub awards (an "NIH Sub Award" and an "Industry Sub Award") between Washington University and each Clinical Center are needed to reimburse the site's research team for its work.

12.2 NIH Sub Award

The Clinical Centers are reimbursed from Washington University funds derived from its NHLBI award. From the NIH Sub Award, three possible payments may be made to the Clinical Center:

1. Initial NIH Payment – $1750 to site PI – all Clinical Centers may receive this payment

   The Initial NIH Payment is triggered by CCC notification of DCC receipt of a complete set of documentation (forms, questionnaires, venogram images) of study assessments performed during screening, enrollment, initial treatment, and early (through 30 days) follow-up:

   - Confirmation of Eligibility CRF
   - Baseline CRF
   - Baseline Compression Ultrasound CRF
   - Baseline Villalta PTS Scale CRFs (Subject & Blinded Clinician)
   - Baseline Leg Pain Severity CRF
   - Baseline Quality of Life Questionnaire CRF
   - Initial Anticoagulation Therapy CRF
   - Initial PCDT Therapy CRF (*PCDT Arm Only)*
   - Pre & Post PCDT Venogram images (*PCDT Arm only*)
   - 10 day & 30 day Follow Up CRFs
   - 30 day Quality of Life Questionnaire CRF
   - 10 day & 30 day Villalta PTS Scale CRFs (Subject & Blinded Clinician)

- 10 day & 30 day Leg Pain Severity CRFs
- 1 Month Compression Ultrasound CRF

2. Substudy Ultrasound NIH Payment - $500 to site PI – only Substudy Centers are eligible

   The Substudy NIH Ultrasound Payment is triggered by CCC notification of VasCore receipt of the Compression Ultrasound Form that documents the 1-year follow-up Substudy Ultrasound Exam along with the corresponding properly labeled exam images or video.
   - Submission of 1 Year Ultrasound Images or Video to VasCore
   - Submission of 1 Year Compression Ultrasound CRF to VasCore

3. Final NIH Payment – $1750 to site PI – all Clinical Centers may receive this payment

   The Final NIH Payment is triggered by CCC notification of DCC receipt of a complete set of data that documents study assessments performed through 2 years of patient follow-up or at the time of documentation of patient death (if applicable), to include CRFs, questionnaires, and source documentation for assessments of PTS and QOL; INR reports, compression therapy compliance; suspected clinical events, adverse events, and changes to DVT therapy; a Cost Diary; and documentation of the reason for exit from the study. A complete set of the CRFs below are due following patient Visits 3-6:
   - Follow Up CRF
   - Quality of Life Questionnaire CRF
   - Villalta PTS Scale CRFs (Subject & Blinded Clinician)
   - Revised CEAP Classification CRF
   - Venous Clinical Severity Score CRF
   - Cost Diary
   - End of Study CRF (*at 24 months or patient withdrawal only*)

   Also, the following CRFs must be submitted when needed, per MOP Section 8.4:
   - Anticoagulation Change CRF
   - Late Endovascular Procedure CRF
   - Adverse Events CRF
   - Serious Adverse Event CRF
   - Suspected Bleeding Event CRF
   - Suspected Venous Thromboembolic Event CRF

- Subsequent Hospitalization CRF
- Death CRF
- End of Study CRF

Each of the above payments includes direct + indirect costs. However, per NIH rules, indirect costs may not be assessed on patient care-related costs such as the costs of the ultrasound exams done at baseline (billed clinically), 1-month follow-up, and 1-year follow-up.

12.3 Industry Sub Award

Supplemental funding for the ATTRACT Trial was obtained from industry sponsors with the specific purpose of reimbursing the non-PI ATTRACT Trial physician co-investigators for their work in coordinating subject enrollment processes, ensuring high visibility and priority of ATTRACT within the Clinical Center, overseeing the medical therapy aspects of protocol execution, and collecting data over the 2-year follow-up period. For Clinical Centers where the endovascular co-investigator is NOT the site PI, these funds may also be used to reimburse the endovascular co-investigator for his/her participation. Two payment types are provided:

1. Multidisciplinary Team Payment - $1000 to site PI

   This payment is triggered by the same deliverables as the Initial NIH Payment.

2. Screen Failure Supplement - $50 per screen failure to site PI

   This payment is triggered by CCC receipt of the DCC's monthly reports which document the screening and non-participation of qualifying potential subjects, defined as patients who meet the study Inclusion Criterion but who are not enrolled because they meet one or more exclusion criteria or decline to participate. This information will be obtained from the Clinical Center's monthly submission of the Screening Log to the DCC.

Note: In general, to be eligible to receive the optional supplementary industry-sourced payments described above, the Clinical Center must agree to abide by the following conditions:

1. Within the Clinical Center, all (100%) of the industry-sourced ATTRACT funds from the Multidisciplinary Team Payment must be allocated to the designated non-PI ATTRACT physician co-investigators from clinical departments that are different from that of the site PI.

2. Each of the following designated physician co-investigators (except for the site PI) must receive at least 25% of the Multidisciplinary Team Payment funds received by the Clinical Center: a) the vascular ultrasound co-investigator; b) the emergency co-investigator; c) the medical co-investigator; and d) the endovascular co-investigator. Site PIs are encouraged to go beyond this minimum requirement and share their funds in a manner which reflects co-investigator contributions and contributes optimally to the success of the study.

3. The site PI must allow the CCC to regularly audit, in HIPAA-compliant fashion, lists of all DVT patients diagnosed at the Center, source documentation for screen failures, and the internal distribution of all ATTRACT funds provided to the Center. The site PI must provide this data to the CCC in a timely fashion upon reasonable request.

12.4 Financial Contacts at the CCC

In this section, the key CCC financial contacts for queries concerning the various subawards or study payments are listed.

For general inquiries about sub awards and payments, please contact:
Colleen Kilbourne-Glynn, MA, CCRP
ATTRACT Trial Project Manager
Mallinckrodt Institute of Radiology
Washington University School of Medicine
660 S. Euclid Ave., Box 8131
St. Louis, MO 63110
Phone: (314) 747-2498
Fax: (314) 747-1944
kilbourne-glynnc@mir.wustl.edu

For specific inquiries about the NIH Sub Award, please contact:
Larry Pyles
Contract Manager
Office of Sponsored Research Services
Washington University in St. Louis
Campus Box 1054
276 N. Skinker Blvd., Suite 220

St. Louis, MO 63130
Phone: (314) 935-5808
Fax: (314) 935-5862
pylesl@wustl.edu

For specific inquiries about the Industry Sub Award, please contact:

Melissa Hengehold-Phillips
Washington University in St. Louis
660 S. Euclid Ave., Campus Box 8009
St. Louis, MO 63110
Phone: (314) 362-2023
Fax: (314) 747-1404
phillipsm@wusm.wustl.edu

13 POLICIES

13.1 Confidentiality

The following study participant confidentiality safeguards should be routinely followed:

- ***Data flow*** – Whenever possible, participants should be identified solely by Subject ID Number. Identifying information should not be transmitted outside the Clinical Center, except for the Medical Billing Release Form (**MOP Appendix L**), which is sent to MAHI, and imaging exams in Centers that cannot de-identify them (both with IRB approval).
- ***Forms*** – ATTRACT Trial forms or pages containing participant identifying information should be separated from other pages of the data forms.
- ***Data disposal*** - Computer listings and other documents that contain ATTRACT participant identifying information should be disposed of in an appropriate manner.
- ***Access*** - Participant records stored in the Clinical Center should not be accessible to persons outside the center without the express written consent of the participant.
- ***Storage*** – ATTRACT Trial forms and related documents retained both during and after study completion should be stored in a secure, fireproof location.
- ***Electronic files*** - Participant identifying information stored electronically should be maintained in an encrypted form or in a separate file.
- ***Passwords*** - Passwords that enable access to study data or participant identifying information should be changed on a regular basis.

- ***User Training*** - Study staff with access to relevant computer systems should be trained in their use and in related security measures. This training should include explanations of how to access the system securely and the importance of system security.
- ***System Testing*** - Prior to the use of a new computer system, and if it is modified, the system should be tested to verify that it performs as expected. Testing should verify that the password approach to system access performs as intended.
- ***System Backups*** - Backup copies of electronic data should be made at specified intervals, and should be stored in areas with limited access. Storage areas should have controlled temperature and humidity so that backup tapes are not damaged.

13.2 Clinical Center Staff Turnover

When new Clinical Center staff join the study, the Delegation of Authority/Responsibility Form must be appropriately revised. The CCC should be notified immediately so that it can ensure that new staff are properly oriented to the study and that all appropriate training is completed. Dr. Vedantham must approve any proposed changes to the site PI or major co-investigators.

13.3 Ancillary Studies

Proposals for Ancillary Studies from ATTRACT investigators should be delivered by e-mail to Dr. Suresh Vedantham, Chair, Operations Committee (vedanthams@mir.wustl.edu). The initial proposal should be formatted as a 2-4 page research summary that contains the following elements: a) the specific aim(s) of the proposed additional research; b) the need for and significance of the project; c) key personnel who would perform the additional work (at least one Steering Committee member should be intimately involved); d) a description of any added work that will need to be done by the Clinical Centers or study personnel; e) the potential impact of the work upon the feasibility of the completing the ATTRACT Trial in a timely fashion – in reviewing the proposal, the Steering Committee will seek to avoid additional burden upon the sites that may interfere with the primary study, so this is very important to critically evaluate; f) any relevant statistical considerations; and g) a plan for funding the additional research.

The Operations Committee will coordinate the initial review and management of Ancillary Study proposals. After its initial review, it will either a) inform the investigator that the proposed study is not acceptable; b) request additional information and/or modification from the investigator; c) forward the proposal to additional Steering Committee members, or to the full Committee, with a request for comment; or d) recommend acceptance of the proposal to the Steering Committee.

Proposals that have been approved by a majority vote of the Operations Committee will then be reviewed by the Steering Committee. To be accepted, an Ancillary Study must be approved by a two-thirds vote of the Steering Committee. If a proposal is approved, a small committee of Steering Committee members will be assigned to work with the proposing investigator to further develop, fund, and execute the proposal within the framework of the ATTRACT Trial as a whole. Publication or presentation of the results of Ancillary Studies is governed by the Publications Policy of the ATTRACT Trial Steering Committee, as outlined in MOP Section 13.4 below.

13.4 Publications

The Publications Policy for the ATTRACT Trial is designed to ensure timely publication of the study results to the appropriate professional audiences; avoid premature publication of results that might compromise the study's performance or its ability to be published in high-impact, high-quality, peer-reviewed medical professional journals; maintain the highest scientific and ethical standards for published materials; and guard against duplicate publication of results. The Steering Committee will follow all DHHS regulations; the NIH Grants Policy Statement, Public Access and Data Sharing Policies; and NHLBI policies on publications and dissemination of data relative to clinical trials. The Steering Committee will provide data to the clinicaltrials.gov registry in accordance with its Policy. Publications and presentations from ATTRACT data will acknowledge the NHLBI's sponsorship and state that their contents are solely the responsibility of the authors and do not necessarily represent the official views of the NHLBI or of the NIH.

Dr. Suresh Vedantham, the Principal Investigator, will coordinate the development of a Steering Committee publications plan. This plan will outline the framework for a primary study manuscript and a number of secondary manuscripts that will be co-authored by writing groups composed of Steering Committee members, corresponding to the pre-specified analyses described in the Protocol. The writing assignments and the initial review and authorship of manuscripts will be determined by a Publications Committee chaired by Dr. Vedantham and consisting of the four Operations Committee members plus Dr. Andrei Kindzelski, the NHLBI Project Officer. Prior to release of the public access dataset, all proposals for presentation or publication of ATTRACT data, and any manuscripts developed, should be sent to Dr. Vedantham, Chair, Publications Committee (vedanthams@mir.wustl.edu). If the proposal or manuscript is approved by the Publications Committee (majority vote), it will be forwarded to the Steering Committee for

review. All proposals or manuscripts must be approved by a two-thirds majority of the Steering Committee prior to submission for peer review. The same process (Publications and Steering Committee review, in sequence) must be followed for re-submission of manuscripts revised in response to peer review, or for proposed public presentations of ATTRACT Trial data.

13.5 Study Website

The ATTRACT study website will be regularly maintained and updated by CCC staff. Upon site initiation, each Clinical Center will be provided with a log-in identification and password to enable its personnel to access the Investigator Resources section of the website. Important study documents, including the most recent versions of the Protocol, MOP, and Case Report Forms will be posted in this area, along with additional educational and training resources that may be useful to research staff. In addition, Clinical Center personnel may gain access to the IRIS and ORCCID sections of the OCOG website using links which are posted on the site.

13.6 MOP Maintenance

This MOP will be maintained and updated periodically throughout the duration of the study by CCC personnel. Each page of the MOP will be numbered, dated, and will display a version number. In this fashion, the MOP will serve as a history of the project, documenting the time and nature of any changes in procedures and policies. The MOP will be continuously reviewed by study staff to ensure its accuracy. If any procedures are subsequently changed or modified, the MOP will be updated and the changes will be distributed to the Clinical Center coordinators.

APPENDIX A - KEY OPERATIONAL CONTACTS

Person	Location	Contact Information
Suresh Vedantham, MD Principal Investigator	CCC	(314) 362-2923 vedanthams@mir.wustl.edu
James R. Duncan, MD, PhD Safety Officer	CCC	(314) 747-6281 duncanj@mir.wustl.edu
Dave Gibson Core Laboratory for Clinical Studies	CCC	(314) 362-7869 dave@im.wustl.edu
Melissa Bellovich Project Coordinator	CCC	(314) 747-2379 bellovichm@mir.wustl.edu
Colleen Kilbourne-Glynn, MA, CCRP Project Manager	CCC	(314) 747-2498 kilbourne-glynnc@mir.wustl.edu
Patty Nieters, RN, BSN Clinical Research Nurse Coordinator	CCC	(314) 362-3371 nietersp@mir.wustl.edu
Mary Clare Derfler, RN, MSN Clinical Research Nurse Coordinator	CCC	(314) 747-2372 derflerm@mir.wustl.edu
Laura Todt, RN, BSN Clinical Research Nurse Coordinator	CCC	(314) 747-8951 todtl@mir.wustl.edu
Marc Filion, MSc Senior Clinical Trial Associate	DCC	(905) 527-2299, ext. 42611 filion@mcmaster.ca
Gail Hadley, RN, RVT Technical Director	VasCore	(617) 726-5552 ghadley1@partners.org
Kate Vilain, MS Research Scientist	MAHI	(816) 932-5480 kvilain@saint-lukes.org
Kathleen Mercure, MHSA Clinical Research Manager	SIR Foundation	(703) 460-5596 kmercure@sirweb.org

APPENDIX B
Form Submission Guide Page 1 – Items to Clinical Coordinating Center

SUBMIT TO CCC	ITEMS
By E-Mail or Fax to: **ATTRACT Research Coordinator** Clare: derflerm@mir.wustl.edu Laura: todtl@mir.wustl.edu Patty: nietersp@mir.wustl.edu Fax: (314) 747-1944	Designation of Team Members Research Team Licenses & CVs Site PI's HIPAA Training Certificate & Protocol Signature Page FDA 1572 Form, FWA Letter, IRB Roster IRB Approval Letter for Protocol Stamped, IRB-Approved ICF & Assent HIPAA Authorization (if separate from ICF) Delegation of Authority/Responsibility Form Institutional UFH Nomogram & Warfarin Monitoring Plan JCAHO/CAP/CLIA Certification & Lab Normals Endovascular Board Certificates & Experience Statement Choice of AngioJet or Trellis
By Expedited E-Mail or Fax to: **Suresh Vedantham, M.D.** vedanthams@mir.wustl.edu Fax to (314) 747-1944 (Within 24 hours of knowledge of event) (Also submit to DCC - see below)	Serious Adverse Event Form Source Documentation for SAEs
By Fax to: **Mary Clare Derfler, RN, MSN** Fax to (314) 747-1944	Drug Request Form
By Fax to: **Dave Gibson, BS** **Core Laboratory for Clinical Studies** Fax to (314) 362-4782	Investigational Drug Accountability Log
By E-Mail to: **Melissa Bellovich** attract@mir.wustl.edu	Advertising Request Form
By Courier Mail to: **Larry Pyles** Contract Manager Office of Sponsored Research Services Washington University in St. Louis Campus Box 1054 276 N. Skinker Blvd., Suite 220 St. Louis, MO 63130	Executed Subaward for NIH-Derived Funds
By Courier Mail to: **Melissa Hengehold-Phillips** Center for Clinical Studies Washington University in St. Louis 660 S. Euclid, Campus Box 8009 St. Louis, MO 63110	Executed Subaward for Industry-Derived Funds

APPENDIX B
Form Submission Guide Page 2 – Items to Data Coordinating Center

SUBMIT TO DCC	ITEMS	AND ALSO:
Submit by ORCCID www.attract.wustl.edu	Adverse Event CRF Anticoagulation Change CRF Baseline CRF Compression Ultrasound CRF Death CRF End of Study CRF Follow-Up CRF Initial Anticoagulation Therapy CRF Initial PCDT CRF Late Endovascular Procedure CRF Leg Pain Severity (Subject) CRF QOL Questionnaire Revised CEAP Classification CRF Serious Adverse Event CRF ►►► Subsequent Hospitalization CRF Suspected Bleeding CRF Suspected VTE CRF Venous Clinical Severity Score CRF Villalta PTS Signs (Blinded Clinician) CRF Villalta PTS Symptoms (Subject) CRF	**Fax to (314) 747-1944 within 24 hr**
Monthly Bulk Courier Mail to: ATTRACT Study Coordinator, OCOG Juravinski Hospital 711 Concession Street, G(60) Wing, 1st floor Hamilton, ON L8V 1C3 CANADA	IRIS Confirmation of Eligibility (original) ► Compression Ultrasound CRF (original) QOL Questionnaire (original) Cost Diaries (original) Villalta PTS Signs (Blind Clinician)(original) Villalta PTS Symptoms (Subject) (original) Venograms & Transmittal Form Ultrasounds & Transmittal Form Suspected Event Transmittal Form Source Documents	**Fax to (905) 575-2639 within 24 hr**

At the beginning of each new month, please FAX the completed Screening Log with the previous month's screening numbers to the DCC at 905-575-2639

APPENDIX B
Form Submission Guide Page 3 – Items to Core Laboratories

SUBMIT TO CORE LABS & PARTNERS	ITEM
Fax to VasCore Fax: (941) 894-6160	US Site Assessment Survey
Mail to VasCore VasCore Attn: Gail Hadley, RN, RVT 62 Staniford Street Boston, MA 02114	Qualifying Compression US Images
Fax and Mail Original to MAHI Fax: (816) 932-4542 Attn: Shawn Smitherman Mid America Heart Institute 4401 Wornall Road HI-5 Room 5627 Kansas City, MO 64111	Patient Accounting Contact Form Medical Billing Release Form
E-Mail to BSN Customer Service attractstudy@bsnmedical.com	Compression Stockings Order Form

APPENDIX C – Sample Warfarin Monitoring Plan

All patients enrolled in the ATTRACT study will be followed in the (insert Center name) hospital by the Vascular Medicine Consult Service. Many physicians who rotate on this service are ATTRACT co-investigators (insert names). All physicians are internists and Vascular Medicine specialists, and many have additional training in either cardiology, hematology, or thrombosis. Anticoagulation will be monitored by this team while in hospital, including the use of heparin nomogram (enclosed), or the use of low molecular weight heparin. Coumadin dosing will be overseen by this group. ATTRACT Control Arm patients who are not admitted to the hospital will receive treatment for acute DVT, generally low molecular weight heparin with coumadin, under the direction of this same team.

Upon hospital discharge, patients enrolled in ATTRACT will be followed in our anticoagulation (Coumadin) program. We use blood lab-based PT/INR test with telephone communication of the Coumadin dosing by our dedicated Vascular Medicine nurses (all RNs) who have extensive experience in anticoagulation management. Patients may have their blood test performed at a (insert Center name) facility (results transmitted to use via EMR) or at an outside lab (results faxed to us). Anticoagulation dosing by the nurses is supervised by the attending staff physicians of our Vascular Medicine group. We generally check INR values no less frequently than once every 4 weeks in stable patients. (Insert medical co-investigator name) will be responsible for overall supervision of anticoagulation for patients enrolled in the ATTRACT study. However, if a patient is cared for by one of the other ATTRACT study co-investigators, the anticoagulation nurses will be directly supervised by that co-investigator and the patient's thrombosis doctor. (Insert medical co-investigator name) will assume direct anticoagulation management supervision for any ATTRACT patient whose physician is not involved in ATTRACT. See below for some guidance our nurses use for dosing Coumadin for stable outpatients. These tools are used as a guideline, and clinical judgment is employed to determine the appropriate dose.

Coumadin Dosing Algorithm Based on Weekly Cumulative Dose
Target INR 2.0 – 3.0
Patient's INR

<1.5	**1.5-1.9**	**2.0-3.0**	**3.1-3.9**	**4.0-4.9**	**≥ 5.0**	
Increase 10-20%. Consider extra dose (a)	Increase 5-10% (a,b)	No change	Decrease 5-10% (c) Consider holding 1	Hold 0-1 days and decrease 10%	Refer to CHEST 2008 guidelines	**Dose Change**
3-5 days	7-14 days	See #3 below	7-14 days	4-8 days		**NEXT INR (May be more frequent per physician discretion)**

(a) Notify physician to determine need for LMWH.
(b) If INR 1.8-1.9, consider no change w/repeat INR in 7-14 days.
(c) If INR 3.1-3.2, consider no change w/repeat INR in 7-14 days.

Remember:

1. Always consider trend in INRs when making warfarin management decisions.
2. Consider repeating INR same day or next day if observed value is markedly different than expected value.
3. For patients with many consecutive therapeutic INRs, INR may be extended to 3-4 weeks.
4. F/U may be accelerated for a single out of range INR.

CHEST Guidelines 2008

Guidelines for Management of Elevated INR and/or Bleeding in Patients Receiving Warfarin/Coumadin®

Warfarin/Coumadin® Reversal Protocol

	INR greater than the upper limits of normal, but < 5	INR ≥ 5 < 9	INR > 9
No Bleeding	• Monitor more frequently • Hold Warfarin (or lower the dose) until INR is in therapeutic range. • If only minimally elevated, no dose reduction may be needed • Restart Warfarin at original or lower dose once INR in therapeutic range.	• Hold Warfarin 1 to 2 doses and monitor more often until the INR is in therapeutic range OR • Omit 1 dose and give vitamin K (1 to 2.5 mgs) orally. • Restart Warfarin at an adjusted dose downward once the INR is in therapeutic range.	• Hold Warfarin until the INR is in the therapeutic range. • Give vitamin K (2.5 to 5 mgs) orally. Monitor more frequently. • Restart Warfarin at an adjusted lower dose once INR is in a therapeutic range.
Rapid Reversal Required	• Discontinue Warfarin. • Give vitamin K (2.5 mgs orally). • Restart Warfarin once the INR is in therapeutic range.	• Discontinue Warfarin. • Give vitamin K (≤ 5 mgs) orally once. Expect an INR reduction within 24 hours.	• Discontinue Warfarin. • Give vitamin K 10 mgs by slow intravenous infusion. • Repeat an INR in 8 hours and give vitamin K based on the INR value and this protocol.
Serious Life Threatening Bleeding	• Discontinue Warfarin. • Give vitamin K 10 mgs by slow intravenous infusion. once. • Repeat vitamin K administration if needed in 12 hours. • Supplement with fresh frozen plasma (FFP) or prothrombin complex (PCC) or recombinant factor VIIa concentrate. • Consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance	• Discontinue Warfarin. • Give vitamin K 10 mgs by slow intravenous infusion once. • Repeat vitamin K administration if needed in 12 hours. • Supplement with fresh frozen plasma (FFP) or prothrombin complex (PCC) or recombinant factor VIIa concentrate. • Consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance	• Discontinue Warfarin. • Give vitamin K 10 mgs by slow intravenous infusion once. • Repeat vitamin K administration if needed in 12 hours. • Supplement with fresh frozen plasma (FFP) or prothrombin complex (PCC) or recombinant factor VIIa concentrate. • Consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the _____Anticoagulation Management Program document as shown below or the CHEST guidelines (CHEST 2008; 133: 160S-198S or 708S-775).

APPENDIX D – Endovascular Statement of Experience

Endovascular Credentialing Information for: _____, M.D.

Below are estimates of the approximate numbers of endovascular DVT thrombolysis procedures that I have performed to treat acute DVT:

____ PCDT utilizing the Angiojet system to deliver thrombolytic drug

____ PCDT utilizing the Trellis system to deliver thrombolytic drug

____ Infusion-first catheter-directed thrombolysis (any slow-infusion catheter)

_____ Other methods of endovascular DVT thrombolysis

Below are estimates of the approximate numbers of lower extremity versus upper extremity thrombolysis treatments that I have provided to treat acute DVT:

_____ Lower extremity (and/or IVC) DVT

_____ Upper extremity (and/or SVC) DVT

Below is an estimate of the number of iliac vein stent placements that I have performed for occlusive lesions identified during the treatment of acute DVT:

_____ Iliac vein stent placements

Below is an estimate of the number of times I have obtained ultrasound-guided venous access for any procedure:

_____ Ultrasound-guided venous access (any)

Below are estimates of the number of times I have obtained ultrasound-guided access into the popliteal vein or a tibial vein for DVT treatment:

____ Ultrasound-guided venous access (popliteal or tibial)

_____ _____

Signature Date

APPENDIX E – Guide to Ultrasound Exams

US EXAM TYPE	PERFORMED BY	ACCEPTABLE WHEN
Baseline Compression US **Perform for Initial DVT Diagnosis** **Bill Clinically**	Preferred: Tech qualified for ATTRACT Compression US Allowed: Any available tech	Performed ≤ 5 days before randomization Documents compression of **ipsilateral** proximal veins Images (preferred) or report reviewed by MD May use only if MD convinced of proximal DVT diagnosis
Repeat Baseline Compression US **Perform if Baseline Exam Not Acceptable** **Bill to Research**	Preferred: Tech qualified for ATTRACT Compression US Allowed: Any available tech	Performed ≤ 5 days before randomization Documents compression of **ipsilateral** proximal veins Preferred: measures CFV & popliteal vein diameters Preferred: documents thrombus extent (drawing) Images (preferred) or report reviewed by MD May enroll only if MD convinced of proximal DVT diagnosis
1-Month Follow-Up Compression US **Perform in All Patients** **Bill to Research**	Preferred: Tech qualified for ATTRACT Compression US Allowed but discouraged: Any available tech	Documents compression of **bilateral** proximal veins Measures bilateral CFV & popliteal vein diameters Documents bilateral thrombus extent (drawing)
Follow-Up Compression US **Perform in Patients with Suspected DVT** **Bill Clinically**	Preferred: Tech qualified for ATTRACT Compression US Allowed: Any available tech	Documents proximal vein compression in **symptomatic leg** Measures CFV & popliteal vein diameters - symptomatic leg Documents thrombus extent (drawing) - symptomatic leg
1-Year Detailed Substudy US **Perform in All Patients in Substudy Centers** **Bill to Research**	Required: Tech qualified for ATTRACT Substudy US	Documents compression of **bilateral** proximal veins Measures bilateral CFV & popliteal vein diameters Documents bilateral thrombus extent (drawing) Documents detailed exam for valvular reflux

APPENDIX F

VasCore
The Vascular Ultrasound Core Laboratory
MASSACHUSETTS GENERAL HOSPITAL

Vascular Core Lab Clinical Site Assessment Survey
ATTRACT Study

PLEASE COMPLETE THE FOLLOWING QUESTIONNAIRE AND RETURN VIA FAX WITHIN 5 BUSINESS DAYS TO: 941-894-6160

Study Name: ATTRACT Study

Site Name: _____ **Site Number**: _____

PI Name: _____

Study Coordinator: _____

Address: _____

_____

_____

Phone #: _____

Fax#: _____

E-mail: _____

- Where will the venous duplex scans be performed for this trial?

  a. office laboratory

  b. hospital based dedicated vascular laboratory

  c. hospital based radiology ultrasound laboratory

  d. hospital based echocardiography laboratory

  e. other:_____

CORE LAB USE ONLY - QUALIFYING EXAMS REQUIRED FOR ALL SITES –(1 COMPLETE BILATERAL VDUS)

Questionnaire Received:___/___/_____ Transcribed to SAS tracker: initial and date:_____
Meets study requirements: YES / NO initials:_____
Site Notified: ___/___/_____

Notes:
_____

VasCore
The Vascular Ultrasound Core Laboratory

- Is the laboratory accredited in PERIPHERAL VENOUS testing?
  YES / NO (ICAVL or ACR)
  if yes, which organization: _____
- Will a credentialed technologist/sonographer perform the venous duplex examinations for this trial?
  YES / NO
- Has this lab previously participated in clinical trials: YES / NO
- How many of the following venous duplex exams are done per month at this lab:

DVT Lower:	a. 1-25	b. 26-50	c. 51-99	d. >100
DVT iliac veins:	a. 1-25	b. 26-50	c. 51-99	d. >100
Standing reflux:	a. 1-25	b. 26-50	c. 51-99	d. >100

- How many years has this lab been performing peripheral venous duplex scans:
  _____yrs.
- List equipment that will be used for the study

  Manufacturer:_____

  Model: _____

  Transducers frequencies available for lower extremity and iliac veins:

  _____

- What type of media will be used to submit the venous duplex exams:

  List all that will be used :_____ _____
- Images must be available through out the course of the study for all visits. Do you have a system in place to retrieve images and submit to the appropriate core lab for review?
  - o YES / NO
- Do you have the ability to burn cineloop clips to a CD or DVD:
  - o YES / NO

VasCore
The Vascular Ultrasound Core Laboratory

Vascular / Ultrasound Laboratory Contact Information

Please complete the following contact information form. It is required to assist the vascular core laboratory in communicating with the sites and the technologist(s)/sonographer(s) participating in this trial.

Site number: _____

Name and address of facility where the exams will be performed:

_____

_____

_____

_____

Please provide a list of all technologists/sonographers that will submit venous studies for the ATTRACT Study.
Include name and credential

Name:_____

Name:_____

Name:_____

Name:_____

Name:_____

Name:_____

Name:_____

Name:_____

Name:_____

Name:_____

Thank you for your assistance

APPENDIX G

Delegation of Authority/Responsibility Form

Site Name_____
Site #_____

STUDY PERSONNEL	SIGNATURE	ROLE	RESPONSIBILITY CODE(s)	START DATE	END DATE	Initial and Date

Role 1=PI 2=Co-Investigator 3=Research Coordinator 4=Pharmacist 5=Regulatory 6=Blinded Clinician (physician or nurse) 7=Vascular Ultrasound Technologist 8=Other (specify in table above)

Delegated Study Responsibilities

1 = Obtain Informed Consent
2 = Screening
3 = Obtain Medical History
4 = Confirmation of eligibility (must be an Investigator)
5 = Subject randomization/enrollment
6 = Performs clinical Assessments
7 = IRB Submission
8 = Regulatory Files Maintenance
9 = Study Drug Dispensing
10 = Study Drug Accountability
11 = Performs US exams
12 = Coordinates Medical Therapy management
13 = CRF Completion
14 = EDC/Electronic Data Capture
15 = Administers QOL Questionnaires
16 = Data Query Resolutions
17 = AE Monitoring / Reporting
18 = SAE Reporting
19 = Performs PCDT
20 = Study Specific Procedures
21 = Other (Specify in Table Above)

Principal Investigator Printed Name _____ Principal Investigator Signature_____ Date_____

Appendix H
CLCS Investigational Drug Accountability Log for the ATTRACT Trial

Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis

Recombinant Tissue Plasminogen Activator / Activase® 50mg

IND Number 103462 National PI: Suresh Vedantham M.D

.LOT # _____

Date Shipment Received Dispensed Destroyed or Returned	**Received** from Genentech or Site **Dispensed Destroyed** If Destroyed/ Why	**Condition of Study Drug on Shipment** Intact/Damaged	**# of Vials** According to Shipment or # Dispensed	**Balance Forward** **Quantity** Actual # Received / Dispensed	**Exp Date**	**Site #**	**Site Name**	**Recorder**

Records kept at the Core Lab for Clinical Studies Washington University in St. Louis

Please FAX Log to Suzanne Doolan at Genentech Upon Receipt of Shipment. FAX 866-817-0365 Contact Suzanne (404)-210-0057 for discrepancies.

APPENDIX I

DRUG REQUEST FORM

Site Name: _____

Site #: _____

PI: _____

Contact Person: _____

Contact Phone: _____

Contact Email: _____

Verify Name and Address of Shipment: _____

_____

_____

_____

_____

_____

Date: _____

Number of Vials Requested: _____

Please FAX this form along with your most recent Investigational Accountability Log to the Clinical Coordinating Center at Washington University in St. Louis at 314-747-1944. You will receive a receipt of fax by email.

FOR CCC Use Only ☐

APPENDIX J

PACKING SLIP from the Core Laboratory for Clinical Studies
Washington University in St. Louis

Study Drug / Recombinant Tissue Plasminogen Activator / Activase® 50mg / rt-PA

Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis

Date	Site #	Site Name	# of Vials in Shipment	Lot #	Exp Date	Fed EX Tracking #	Initials	CLCS use only/ Initial and Date to Confirm Receipt at Site

Please complete the Investigational Drug Accountability Log at your Site following Receipt of Study Drug.
Fax the Investigational Drug Accountability Log to the Core Lab for Clinical Studies (CLCS) Fax 314-362-4782 within 24 hours of receipt.
Contact David Gibson at 314-362-7869 if a vial is damaged upon receipt or a discrepancy is noted. Fax the Investigational Drug Accountability Log to the CLCS noting this discrepancy.

APPENDIX K
Investigational Drug Accountability Log

Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis

Site Name: _____

Site # _____ **IRB# / HRPO#** _____

Investigator: _____

Recombinant Tissue Plasminogen Activator / Activase® 50mg

Do Not Fill Prescription Without A Subject Identification Number

Date Shipment Received, Dispensed or Destroyed	**Subject Identification Number (if drug being dispensed)**	**Received / Dispensed** or **Destroyed** (If destroyed why)	**# of Vials** According to Shipment or # Dispensed	**Balance Forward** **Quantity** Actual # Received/ Dispensed	**Condition of Study Drug on Receipt** Intact/Damaged	**Lot #**	**Expiration Date**	**Recorder**

Please FAX this form to The Core Lab for Clinical Studies (314)-362-4782 within 24 hours upon receipt of shipment or when medication dispensed or destroyed. Please call David Gibson (314)-362-7869 if a vial is damaged upon receipt or a discrepancy is noted.

APPENDIX L

ATTRACT Trial

Economic Study Procedures

TO: **ATTRACT Trial Study Coordinators**

FROM: Kate Robertus, Research Scientist
Elizabeth Mahoney, ScD, Director
Health Economics and Technology Assessment Group (HETA)

SUBJECT: **ATTRACT Economic Study**

The ATTRACT Trial includes an **Economic** component. This start-up packet provides a brief overview of this component along with instructions to help make both of these studies a success at your hospital.

Included in this packet are the following:

- **Introduction** to the **Economic** component of the ATTRACT trial
- **Informed Consent information**
- **Information regarding your IRB submission**
- **Detailed instructions for the Economic study**
- **Questions & Answers**
- **Appendix A- HIPAA regulations**

I look forward to working with you throughout the duration of the trial. If you have any questions or concerns, please do not hesitate to contact me at (816) 932-5480 or at krobertus@saint-lukes.org or Elizabeth Mahoney at (816) 932-8235 or at emahoney1@saint-lukes.org.

Sincerely,

Kate Robertus

ATTRACT CLINICAL TRIAL
Procedures for Economic Study

Overview

Throughout this trial, medical resource use data along with clinical data will be collected by the Research Coordinator using case report forms. In addition, UB-04 forms and itemized hospital bills will be collected directly from participating non-VA hospitals by the HETA team at MAHI. Prior to enrollment in the study, non-VA patients will be asked to provide personal information and permission to obtain medical billing records for the length of their follow-up period. All related data will be kept in a secure and confidential database.

Study Coordinator's Responsibilities:

1. Informed Consent:

Important- Please ensure that your informed consent contains the following language pertaining to the economic and quality of life studies before it is submitted to your IRB:

Economic Study

In conjunction with the clinical study, a separate evaluation of the economic costs and benefits of treatment will be measured in a sub-study by assessing the cost of both: (a) the PCDT deep-vein thrombosis treatment and DVT-related hospitalizations in the TREATMENT group, as compared with the cost of (b) standard CDT treatment and DVT-related hospitalizations in the CONTROL group at various time points during follow-up. As part of this study, patients will be asked to sign a Medical Billing Release form. This form will be used by the Health Economics and Technology Assessment (HETA) Group of the Mid America Heart Institute (MAHI) in Kansas City, Missouri, to collect hospital bills from the patient accounting department at any hospital to which patients are admitted, from the time of enrollment in the study through the study follow-up period. This information will be kept strictly confidential and be used solely to assess the medical expenses that occur during the course of this study.

ATTRACT CLINICAL TRIAL
Procedures for Economic Study
(U.S., Non-VA sites only)

2. Submitting to your IRB

Many hospitals require that the Medical Billing Release form be approved by their IRB before this form can be used in the study. If this is the case at your institution, please make sure that this authorization form is submitted to your IRB with the rest of your ATTRACT documents before the start of the study. Please see the following sections for more information on this form and its purpose in the study.

3. Patient Accounting Contact

Establish a specific contact person in the Patient Accounting Department, complete the Patient Accounting Contact Form on the next page, and FAX it to MAHI.

Inform the Patient Accounting Contact that they will be receiving a letter and a follow-up phone call from MAHI regarding the hospital bills we will need for the ATTRACT Trial.

4. Patient Cost Diaries

The cost diaries, available in English and Spanish, are booklets intended to serve as a memory aid for patients when they are asked about any medical care use during a follow-up visit or call. The diaries contain instructions on how to record any medical visits, including outpatient visits, hospitalizations, and other expenses, such as stockings or walkers, related to their leg problem, since the previous study visit. It is important that you are familiar with the booklet format and can show patients how to fill it out at their 10-day visit. Patients should be instructed to try to bring their booklets to all study visits.

The cost diaries are **not official data collection tools that will be analyzed -- that is the purpose of the CRFs. The data in the diaries should not be simply copied into the CRFs**, but used to remind the patient about medical visits and other specific expenses at follow-up visits while you are filling out the Follow-Up CRF. After a study visit and completion of the Follow-Up form using the cost diary as a prompt, collect the old diary and provide the patient with a new one. Mail collected, de-identified diaries to the Data Coordinating Center (DCC) at McMaster University. The DCC will send the diaries to MAHI. Let the Clinical Coordinating Center (CCC) at Washington University know when booklets are running low at your site.

That's it! The HETA team will do the rest!

Mid America Heart Institute
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Directed by Cardiovascular Consultants, P.A.
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TO: **ATTRACT Trial Study Coordinators**

FROM: Shawn Smitherman, Research Associate
Kate Robertus, Research Scientist
Elizabeth Mahoney, ScD, Director
Health Economics and Technology Assessment Group (HETA)

SUBJECT: **ATTRACT Trial Patient Accounting Contact**

DATE: October 16, 2008

As part of the **ATTRACT Trial** economic study, we need a contact person from each site's patient accounting department. We will be sending a list of the patients whose hospital bills we need directly to the patient accounting contact each month.

Please complete the information below and fax it to Shawn Smitherman at 816/932-4542.

_____ _____
Site # Site Name

_____ _____
Name of Patient Accounting Contact Phone number

_____ _____
E-mail address of Patient Accounting Contact FAX number

_____
Name of Research Coordinator

_____
E-mail address of Research Coordinator

If you run into difficulties or have questions, please contact Kate Robertus at (816) 932-5480 or via email at *krobertus@saint-lukes.org* or Elizabeth Mahoney at (816) 932-8235 or via email at *emahoney1@saint-lukes.org*

ATTRACT CLINICAL TRIAL
Procedures for Economic Study

Medical Billing Release form & HIPAA

- By completing and signing the ATTRACT Medical Billing Release (MBR) form (see sample on the next page), patients in the trial provide their personal information to MAHI and provide consent that this information can be used to collect hospital billing records through the end of their follow-up period.

- Because of the private nature of the information collected, it is necessary that the MBR authorization form adhere to the guidelines set forth by HIPAA. These required components of a HIPAA authorization, and their place in the content of the MBR form, are described in Appendix A.

- Instructions: The Medical Billing Release form must be:

    1. Filled in completely at the time of the patient's consent. Fields for the patient's Medical Record number and Social Security number must be filled in.

    2. Signed and dated by the patient or proxy.

    3. FAXED directly to the HETA Group at MAHI by the patient's hospital discharge. Attention: Shawn Smitherman at (816) 932-4542.

    4. One photocopy should be given to the patient, and a second copy should be kept on site.

    5. Original copy should then be MAILED to the HETA group to the address listed on the form.

Note: If for any reason a patient refuses to sign the Medical Billing Release Form, please complete the header with the Site # and Patient # and write "Patient Refused" across the remainder of the form. Follow the above directions for FAXing and mailing this form to us.

Site ID: _____	Subject ID: _____	Subject Initials: ____ ____ ____

Medical Billing Release Form

1. Patient's Name: _____

2. Date of Birth _____/_____/_____ (mm/dd/yyyy)

3. Patient's Medical Record Number: _____
(At enrolling hospital)

4. Social Security Number: _____ - _____ - _____

The ATTRACT Trial will gather data in order to compare the medical care costs for patients with deep-vein thrombosis (DVT) treated with PCDT vs. standard DVT management. By signing this form, I authorize the staff/representatives of the Health Economics and Technology Assessment Group of the Mid America Heart Institute (MAHI) to use the above information [Patient's Name, Date of Birth, Medical Record Number and Social Security Number] to collect my medical bills for any patient visits or hospitalizations that begin during my time in the ATTRACT study. In doing so, I authorize the Patient Accounting Department at any hospital where I receive care during this time period to disclose these billing records to MAHI. I understand that this information collected by MAHI will be kept strictly confidential and be used solely to assess the reasonable medical expenses that occur during the course of the ATTRACT Trial. The information will not be re-disclosed to any outside party. Additionally, I understand that I have the right to 1) refuse to sign this document, 2) withdraw this authorization at any time by giving written notice to the address listed at the bottom of this form, with the knowledge that this action will not affect any information collected before the notice of withdrawal, and 3) receive a copy of this authorization.

5. This billing information may be collected for patient visits or hospitalizations that begin between

_____ (study enrollment date) and _____ (2 years from

date of enrollment).

6. Signature: _____ ☐ (1) patient
☐ (2) proxy _____
(relationship)

7. Research Coordinator: _____
(Signature)

_____
(Please print name)

8. RC Phone Number: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
(At enrolling hospital)

Date Signed: _____/_____/_____ (mm/dd/yyyy)

Research Coordinator: Please FAX under separate cover and then MAIL original form to the HETA Group at MAHI. Please give one copy of this consent to the patient and keep a copy in your records. FAX: (816) 932-4542; Attn: Shawn Smitherman, Mid America Heart Institute, 4401 Wornall Road, HI-5 Room 5627, Kansas City, MO 64111.

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TO: **Study Coordinators / I.R.B.**

FROM: Kate Robertus, Research Scientist
Elizabeth Mahoney, ScD, Director
Health Economics and Technology Assessment Group (HETA)

SUBJECT: **ATTRACT Economic Study - Subject Confidentiality Procedures**

DATE: October 16, 2008

The Health Economics and Technology Assessment (HETA) team adheres to the following guidelines to ensure the confidentiality of all patient information:

- The Medical Billing Release form is created to be compliant with all HIPAA regulations.
- All Medical Billing Release forms and/or patient bills mailed to MAHI will be delivered directly to the appropriate HETA team member by the mailroom.
- Personal information collected on the Medical Billing Release form will be entered into a highly secured database at MAHI, separate from all clinical data, and this information will be used solely to request outstanding bills.
- All Medical Billing Release forms received at MAHI will be stored by trial/site/patient number in a locked file cabinet within the HETA office space. The HETA Manager, Research Associate, and Project Assistant are the only people who will have access to the file cabinet. No clinical data will be stored with these documents.
- All itemized and UB-04 Bills received at MAHI will be labeled with the following information: Study Name, Site Number, Patient Number, and Initials. Once this information has been recorded on the bill, the patient name, address, and any additional personal information will be blacked out by the HETA team. Bills will be stored by study/site/patient number in locked file cabinets within HETA office space. No clinical data will be stored with these documents.

If you have any questions or comments, please contact
Kate Robertus at (816) 932-5480 or via email at krobertus@saint-lukes.org
or Elizabeth Mahoney at (816) 932-8235 or via email at emahoney1@saintlukes.org.

ATTRACT CLINICAL TRIAL
Procedures for Economic Study

Questions and Answers:

How is confidentiality maintained?
Patient Confidentiality is given the highest priority at HETA. Billing information is used only to extract the cost of procedures. Our database is highly secured and separate from clinical data. All paper information is stored in a locked file cabinet. Only three HETA members working on the ATTRACT Trial have access to the file cabinet and the billing information. See confidentiality procedures memo in this packet for more detailed information.

My facility will not release patient names. Can we still participate?
Yes. Direct bill collection by HETA is meant to save time for coordinators. In order to use this method of bill collection patient names must be used. If your facility will not release names, Research Coordinators can collect billing information, black out patient names and send bills for patients' initial hospitalization and any subsequent hospitalizations to HETA. Should this occur, please contact the HETA team as soon as possible to alert them of the situation. You will then receive separate instructions on how to reword your informed consent, collect bills from the accounting department, label them, and forward them to MAHI.

If the patient is transferred or readmitted to another hospital, do I have to contact that hospital and get the billing information?
For the majority of sites, no. If a patient is transferred or readmitted to another hospital, simply fill out the Subsequent Hospitalization case report form for this readmission. HETA will contact the other hospital and use the Medical Billing Release form to collect the billing information. ***** However, if your site will not allow HETA to collect bills directly, you will be responsible for contacting all outside hospitals and requesting the necessary billing information.

If the patient is admitted at a hospital and is subsequently transferred to a second hospital, how many Subsequent Hospitalization forms should I fill out?
If a patient is admitted to a hospital and then transferred to a second hospital, either that same day or on another day, you should fill out two Subsequent Hospitalization forms.

Can I send a copy of the Medical Billing Release form to MAHI and keep the originally signed copy in the patient file?
No, since the HETA group will be responsible for collecting bills directly, we need the originally signed copy of the Medical Billing Release Form in our files. Please FAX the form, and then send the original to Bekah Case, to the FAX number and address found on the Medical Billing Release form. You should provide the patient with one copy and keep a second copy in your records. The Medical Billing Release Form should be kept separate from your completed case report forms.

ATTRACT CLINICAL TRIAL
Procedures for Economic Study

Appendix A- HIPAA Regulations

The following table contains the required information necessary in a HIPAA-compliant authorization form, and where to find the language in the MBR form that satisfies this requirement:

HIPAA requires a statement of…	**Excerpt from MBR to comply with this requirement:**
-What information will be used or disclosed	"… I authorize…MAHI…to use the above information [Patient's Name, Date of Birth, Medical Record Number, and Social Security number]…" "…I authorize the Patient Accounting Department at any hospital where I receive care during this time period to disclose these billing records to MAHI."
-The purpose of the requested use or disclosure	" The ATTRACT Trial will gather data in order to compare the medical care costs for patients with deep-vein thrombosis (DVT) treated with PCDT vs. standard DVT management."
-Who may disclose the information	"…I authorize the Patient Accounting Department at any hospital where I receive care during this time period to disclose these billing records to MAHI."
-To whom the information will be disclosed.	"…I authorize the Patient Accounting Department at any hospital where I receive care during this time period to disclose these billing records to MAHI." "The information will not be re-disclosed to any outside party."
-The patient's right to refuse to sign the authorization	"…I understand that I have the right to: 1) refuse to sign this document"
-The patient's right to revoke the authorization	[I understand that I have the right to:] "2) withdraw this authorization at any time by giving written notice to the address listed at the bottom of this form, with the knowledge that this action will not affect any information collected before the notice of withdrawal"
-The patient's right to receive a copy of the authorization	[I understand that I have the right to:] "3) receive a copy of this authorization."
In addition, the HIPAA compliant authorization must…	
- contain an expiration date.	"This billing information may be collected from (study enrollment date) up to (5 years from date of enrollment)"
- contain an individual's or proxy's signature and date.	"Signature: _____ ❑ (1) patient ❑ (2) proxy_____ (relationship)"
- be written in plain language.	The MBR form is written clearly in plain language for the patient to understand.

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HETA Contact for ATTRACT CLINICAL TRIAL

Shawn Smitherman, Research Associate

Health Economics and Technology Assessment Group

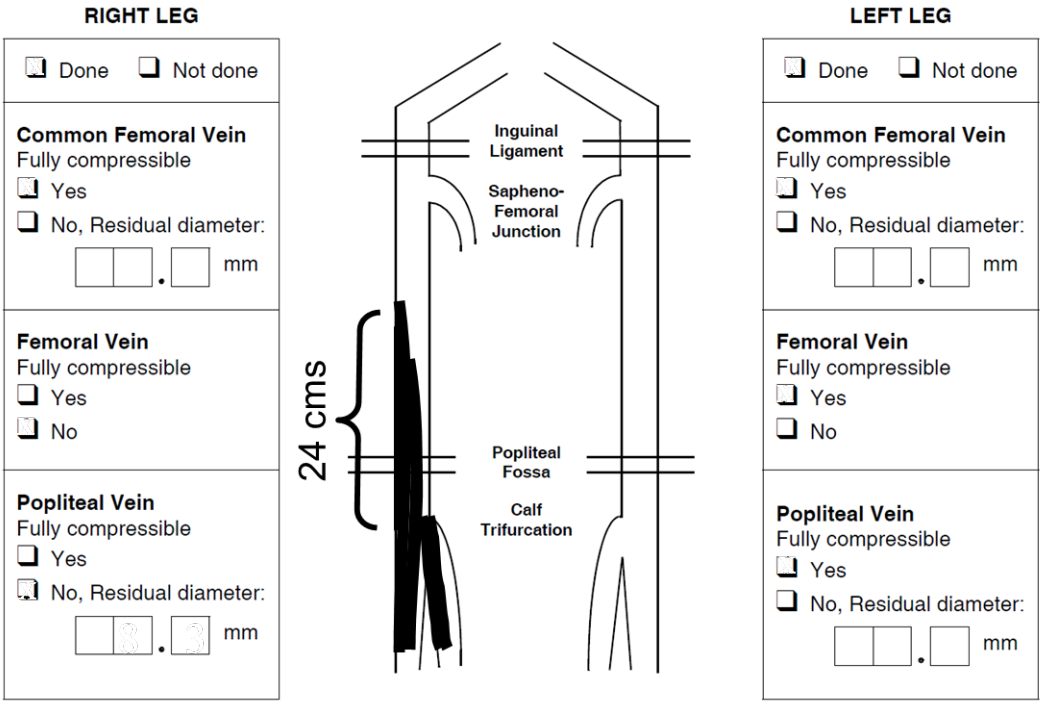
Mid America Heart Institute of St Luke's Hospital

4401 Wornall Road, HI-5, room 5616

Kansas City, MO 64111

Ph: (816) 932-0394
Fax: (816) 932-4542
Email: ssmitherman@saint-lukes.org

APPENDIX M – Sample Compression Ultrasound Form Completion
ATTRACT Trial



In the above patient, a compression ultrasound (US) examination was performed to evaluate the proximal deep veins in both lower extremities. The findings and documentation are as follows:

RIGHT LEG: The exam revealed thrombosis in the deep veins of the right leg. The right common femoral vein was fully compressible (see checked "Yes" box). The lack of full compressibility of the distal part of the right femoral vein, popliteal vein, and calf vein trifurcation are documented by checking of the respective "No" boxes. The residual diameter of the mid-popliteal vein was measured during compression at 8.3 mm – this was entered in the adjacent boxes. To clearly depict the anatomic extent of thrombus, the involved venous segments were shaded on the diagram. The upper margin of the thrombus is located 24 cm from the calf vein trifurcation – this measurement was made and written onto the CRF with brackets indicating exactly what area was measured. This clear documentation of thrombus extent will enable accurate comparison with a future exam.

LEFT LEG: The left leg veins were fully compressible (see checked "Yes" boxes for left common femoral vein, femoral vein, and popliteal vein, and the lack of shading of any venous segments on the diagram.

Appendix N - Site Regulatory Binder Contents

1. ATTRACT Trial Directory	▸ Key Operational Contacts for the ATTRACT Trial ▸ All Contact Information from your site including the Principal investigator, all Co-Investigators, Research Coordinator(s), Pharmacist, and all site staff involved in the ATTRACT Trial
2. Screening and Enrollment	▸ Screening Log ▸ Monthly Enrollment Reports from the Data Coordinating Center
3. FDA Approval Letter	▸ IND letter dated 10/3/08 ▸ Correspondence
4. FDA 1572	▸ FDA 1572 (Initial and all updated forms)
5. IRB Initial Approval Letter	▸ Initial Notification of Approval
6. IRB Approved Current Protocol	▸ Protocol ▸ Signature Page for the Protocol and Investigator's Brochure
7. Informed Consent (English)	▸ IRB Approved Versions of ICF (English) Adult ▸ IRB Approved Versions of ICF (English) Minor ▸ HIPAA Authorization (If a separate document from the ICF)
8. Informed Consent (Spanish)	▸ IRB Approved Versions of ICF (Spanish) Adult ▸ IRB Approved Versions of ICF (Spanish) Minor ▸ HIPAA Authorization (If a separate document from the ICF)

Appendix N - Site Regulatory Binder Contents

9. IRB Approved Advertising Materials	▸ IRB Approval letters for the patient brochure, poster, and/or any other materials used for advertising the study, per your IRB's regulations.
10. Protocol Amendments/IRB Approval Letters	▸ IRB approval letter for all protocol amendments ▸ PI Signature page for all amendments
11. IRB Submission Forms /Contingency letters	▸ IRB correspondence—letters of submission and approval notices
12. Annual IRB Renewal	▸ Progress Reports and annual IRB renewals ▸ Annual Renewal of Protocol ▸ Annual Renewal of ICF
13. IRB Communication	▸ SOP for reporting AEs and SAEs at your Center ▸ *IRB notification for & responses to SAE reports. ▸ Close out/final report notice *(If filed elsewhere please provide memo stating location of the SAE forms – e.g. patient binder)
14. IRB Roster/FWA	▸ IRB membership information ▸ Federal Wide Assurance
15. Certification/Human Subject Protection	▸ NIH mandated education and training documentation on human subject protection for all investigators and research team members
16. Curriculum Vitae (CV) / Licenses	▸ Signed, dated CVs for PI, all Co-Investigators, and site staff (updated every two years) ▸ Current medical license, medical specialty, and board certification number (if applicable) for all Principal and Co-investigators

Appendix N - Site Regulatory Binder Contents

17. Financial Disclosure	▸ Annual Financial Disclosure Statement from all investigators listed on the 1572
18. Delegation of Authority Log	▸ This is the study personnel responsibility list. This log includes: name, signature, initials and delegated study related tasks of all individuals involved in the trial.
19. Investigator Brochure	▸ Activase® Investigator Brochure ▸ Activase® Package Insert
20. IND Safety Reports	▸ SOP for reporting IND Safety Reports to your IRB ▸ IND Safety Reports ▸ IRB notification of & response to Safety Reports
21. Laboratory	▸ Laboratory accreditation/certification CAP/ CLIA Certifications ▸ Lab normal ranges for all tests performed in study ▸ Lab Director's CV and Medical License
22. Endovascular Therapy Credentialing	▸ Endovascular Co-Investigator Statement of Experience ▸ Endovascular Co-Investigator Sub-Specialty Board Certificate(s) ▸ CCC Letter - Endovascular Therapy Certification ▸ Site's device selection for initial PCDT therapy
23. Medical Therapy Credentialing	▸ Unfractionated Heparin Nomogram Plan ▸ Warfarin Monitoring Plan ▸ CCC Letter – Medical Therapy Certification

Appendix N - Site Regulatory Binder Contents

24. VasCore (Ultrasound Core Lab)	▸ Site Assessment Survey (SAS) ▸ CCC Letter - Ultrasound Certification ▸ Correspondence
25. MAHI Health Economic	▸ MAHI Medical Billing Release Form ▸ Correspondence
26. Site Monitoring	▸ Site Initiation Visit Log ▸ Site Monitoring Visit Log ▸ CCC Site Initiation & Monitoring Reports ▸ Site Close Out Visit Report (if applicable) ▸ Protocol Violation Reports (if applicable)
27. DSMB Correspondence	▸ Correspondence
28. Case Report Forms	▸ Blank set of Case Report Forms
29. Drug Accountability	▸ Investigational Drug Accountability Log ▸ Packing Slip ▸ Drug Request Form ▸ SOP for Drug Destruction at your site. If the contents filed elsewhere (e.g. pharmacy), please provide memo stating where. At Trial completion, please place all records here in the regulatory binder.
30. Site Correspondence	▸ Other Study related communication (letters, memos, written documentation of telephone conversations, facsimiles, newsletters, copies of electronic correspondence with the CCC and DCC

Appendix O - Patient Binder Contents
ATTRACT Trial

1. Documentation of Informed Consent
2. Documentation of Child Assent (minors only)
3. HIPAA Authorization (if separate from ICF)
4. Signed Medical Billing Release Form (Copy)
5. Confirmation of Eligibility Form
6. Worksheets or Source Documents if created
7. Case Report Forms completed at Baseline
    a. Baseline Form
    b. Compression Ultrasound Form (baseline exam)
    c. Villalta PTS Symptoms (Subject) Form
    d. Villalta PTS Signs (Blinded Clinician) Form
    e. Leg Pain Severity Form
    f. Quality of Life Questionnaire (Subject)
8. CD (copy) with Baseline Compression Ultrasound exam images
9. Initial Anticoagulation Therapy Form
10. Initial PCDT Therapy Form (Experimental Arm patients only)
11. CD (copy) with pre-PCDT and post-PCDT venogram images (Experimental Arm only)
12. Case Report Forms completed at 10-Day Follow-Up Visit
    a. Follow-Up Form
    b. Leg Pain Severity (Subject) Form
    c. Villalta PTS Signs (Blinded Clinician) Form
    d. Villalta PTS Symptoms (Subject) Form
13. Case Report Forms completed at 30-Day Follow-Up Visit
    a. Follow-Up Form
    b. Leg Pain Severity (Subject) Form
    c. Quality of Life Questionnaire (Subject)
    d. Villalta PTS Signs (Blinded Clinician) Form
    e. Villalta PTS Symptoms (Subject) Form
    f. Compression Ultrasound Form (30-day exam)
14. CD (copy) with 30-day Follow-Up Compression Ultrasound exam images
15. Case Report Forms completed at 6-Month Follow-Up Visit
    a. Follow-Up Form
    b. Quality of Life Questionnaire (Subject)

Appendix O - Patient Binder Contents
ATTRACT Trial

c. Revised CEAP Classification (Blinded Clinician) Form
d. Venous Clinical Severity Score-VCSS (Blinded Clinician) Form
e. Villalta PTS Signs (Blinded Clinician) Form
f. Villalta PTS Symptoms (Subject) Form

16. Case Report Forms completed at 12-Month Follow-Up Visit
    a. Follow-Up Form
    b. Quality of Life Questionnaire (Subject)
    c. Revised CEAP Classification (Blinded Clinician) Form
    d. Venous Clinical Severity Score-VCSS (Blinded Clinician) Form
    e. Villalta PTS Signs (Blinded Clinician) Form
    f. Villalta PTS Symptoms (Subject) Form
    g. Compression Ultrasound Form (Substudy Exam – Substudy Centers only)
17. Case Report Forms completed at 18-Month Follow-Up Visit
    a. Follow-Up Form
    b. Quality of Life Questionnaire (Subject)
    c. Revised CEAP Classification (Blinded Clinician) Form
    d. Venous Clinical Severity Score-VCSS (Blinded Clinician) Form
    e. Villalta PTS Signs (Blinded Clinician) Form
    f. Villalta PTS Symptoms (Subject) Form
18. Case Report Forms completed at 24-Month Follow-Up Visit
    a. Follow-Up Form
    b. Quality of Life Questionnaire (Subject)
    c. Revised CEAP Classification (Blinded Clinician) Form
    d. Venous Clinical Severity Score-VCSS (Blinded Clinician) Form
    e. Villalta PTS Signs (Blinded Clinician) Form
    f. Villalta PTS Symptoms (Subject) Form
    g. End of Study Form
19. Case Report Form for Unscheduled Visits:
    a. Follow-Up Form
20. Supplementary Case Report Forms completed as prompted by clinical status
    a. Adverse Event Form
    b. Serious Adverse Event Form
    c. Late Endovascular Procedure Form

d. Anticoagulation Change Form
e. Subsequent Hospitalization Form
f. Suspected Bleeding Event Form
g. Suspected Venous Thromboembolic Event Form
h. Death Form
i. End of Study Form
j. Compression Ultrasound Form (for US exams to assess for recurrent DVT)
k. Villalta PTS Signs (Blinded Clinician) Form – if late endovascular procedure planned
l. Villalta PTS Symptoms (Subject) Form – if late endovascular procedure planned
m. Quality of Life Questionnaire (Subject) – if late endovascular procedure planned

21. CDs (copies) with Compression Ultrasound exam images (suspected clinical event exams)
22. Source Documents, as needed, to accompany each CRF submission