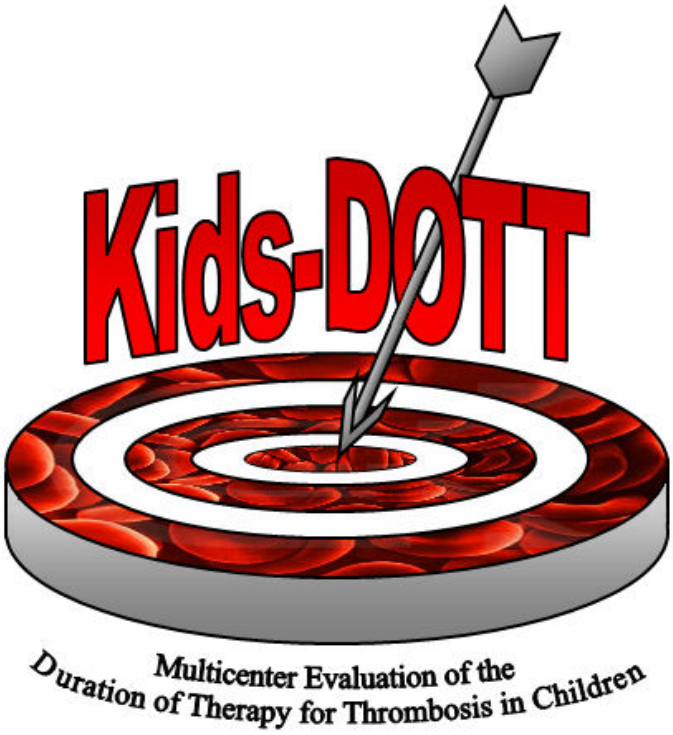


Manual of Operations
Version 9: 4/14/2021

Principal Investigator: Neil A. Goldenberg, MD, PhD

1. TABLE OF CONTENTS

2. GETTING STARTED

Dear Kids-DOTT Trial Investigator and Clinical Research Coordinator,

Thank you for your enthusiasm to participate in the Kids-DOTT trial, a multicenter, parallel-cohort randomized controlled clinical trial (RCT) evaluating the duration of anticoagulant therapy for first-episode venous thrombosis in children [Goldenberg NA et al., Contemp Clin Trials 2010].

The Kids-DOTT trial is funded by a grant from National Institutes of Health (NIH) National Heart, Lung, and Blood Institute, All Children's Hospital Johns Hopkins Medicine and All Children's Hospital Foundation. This study was previously funded by an NIH career development award, an Investigator-initiated study award through industry, and a seed grant from the Hemophilia and Thrombosis Research Society. It is the first pediatric trial to incorporate standardized post-thrombotic syndrome assessment as a key outcome, in addition to conventional primary endpoints of recurrent venous thromboembolism (efficacy) and clinically-relevant bleeding (safety). The primary analysis is innovative in using a bivariate endpoint approach to model the inherent tradeoff between these two outcomes, from a net-clinical-benefit perspective [Kittelson J et al., J Thromb Haemost 2013].

Beyond its principal hypothesis on duration of therapy, Kids-DOTT tracks efficacy and safety across a variety of anticoagulants (none of which have Food and Drug Administration (FDA)-approved "indications" in treatment of pediatric venous thrombosis). The trial also investigates predictors of outcome in pediatric venous thrombosis, utilizing both clinical factors and biologic factors (that latter including novel proteomic and genomic biomarkers and global assays of coagulation and/or fibrinolysis.

The protocol design of Kids-DOTT is pragmatic and, having been developed with input from multiple Investigators nationally, is structured upon a consensus of best clinical care in this disease. Nevertheless, given feasibility challenges faced by RCTs in pediatric venous thrombosis, as well as the large scope of Kids-DOTT, the first stage of the trial is an internal pilot aimed at demonstrating suitable protocol adherence, inter-rater reliability between local and central radiology interpretation, and pace of multi-site enrollment. Upon successful completion of the pilot phase (first n=100 subjects), patient accrual on Kids-DOTT continued seamlessly, as all data are rolled into the definitive trial.

Throughout its course, independent oversight of safety reporting and data quality assurance in Kids-DOTT is provided in collaboration with CPC Clinical Research, a university-affiliated academic research organization that also serves as the Data Coordinating Center for the trial. The Clinical Coordinating Center is Johns Hopkins All Children's Hospital (St. Petersburg, FL). The Executive Steering Committee is comprised of established leading trialists in the pediatric and adult VTE and cardiovascular fields, including Sam Schulman, MD, PhD (McMaster), Will Hiatt, MD (University of Colorado), Craig Kessler, MD (Georgetown), Alex Spyropoulos, MD (Hofstra), Jonathan Halperin, MD (Mount Sinai), John Kittelson, PhD (University of Colorado), Graham Turpie, MD (McMaster), Gabriel Steg, MD (University of Paris), Marilyn Manco-Johnson, MD (University of Colorado), and Tom Abshire, MD (Blood Center of Wisconsin).

We are excited to have you aboard, and look forward to making great strides together in advancing the field of pediatric venous thromboembolism.

Sincerely,

Neil Goldenberg, MD, PhD

3. CONTACT INFORMATION

Central Site Contacts			
Overall Multi-center Study PI	Neil Goldenberg, MD PHD	727-767-2443	Neil@jhmi.edu
CCC Senior Project Manager	Frances Hamblin	727-767-2460	Frances.Hamblin@jhmi.edu
CCC Project Manager	Laurel McDevitt	727-767-6886	Laurel@jhmi.edu
JHAC Pediatric Biorepository		727-767-2450	allkidsbiorepository@jhmi.edu
Grants and Contracts/Invoicing	Sandy Wismer	727-767-4813	Swismer1@jhmi.edu

4. STAFF TRAINING

4.1 Human Subjects Protection and Good Clinical Practice Training

All study staff will provide documentation of completion of:

- Biomedical Investigators Basic Human Subjects Protections Course
- Health Insurance Portability and Accountability Act (HIPAA) Certification

These trainings can be institution specific or through the CITI training program. The CITI trainings are available at no cost online at https://www.citiprogram.org/.

These trainings must be renewed as per local institutional review board (IRB) requirements. Copies of the trainings should be kept in the site's regulatory binder as well as sent to the coordinating center via the site's primary project manager.

4.2 Protocol Training

A site initiation teleconference/webinar will be completed during site start up, and interim teleconferences/webinars/training will be conducted for reinforcement of training on protocol and study procedures as needed. Documentation should be kept by the site to document all study staff training in the site's regulatory binder. The Trial Master File will also contain an attendance record for each teleconference.

4.3 Study Specific Training

All study staff will have training on study procedures based on the delegation of tasks log to include:

- Consenting and HIPAA
- Lab collection, processing and shipment
- Pediatric Post-Thrombotic Syndrome (PTS) Outcome Instrument Completion
    - Delegated staff should be chosen based upon clinical skill in clinical assessment (e.g., hemophilia physical therapist, oncology nurse) and ability of this individual to remain

blinded to treatment arm (i.e. duration of therapy) and affected limb —hence, not a clinician involved in the direct care of thrombosis patients. This individual must complete video-based training on standardized PTS assessment, complete the post-training quiz and send the completed quiz to the Clinical Coordinating Center (CCC) for scoring. A score of 80% must be achieved prior to certification by the Coordinating Center for PTS assessment in the trial. Training and satisfactory completion of the quiz should be repeated annually to maintain competency.

- Radiological Assessments
- Physical Exam
- Data Entry
- Reviewing and reporting adverse events
- Regulatory submissions
- Maintenance of site regulatory documentation

Documentation of completion of training will be kept in the study Regulatory Document binder.

5. STUDY MATERIALS

5.1 Regulatory Binder

It is the responsibility of the site to ensure that their site's Regulatory Binder is maintained. The Regulatory Binder should contain the following documentation:

- Delegation Log
- Investigator of Record Form
- Protocol, IRB-approved
- Protocol Signature Page
- Informed Consent, IRB-approved
- HIPAA authorization (if separate from informed consent)
- IRB Correspondence including all approvals
- Manual of Operations
- Lab Manual
- CVs/Medical Licenses
- Contract
- Screening and Enrollment Log
- Adverse event (AE)/Serious adverse event (SAE) Reports
- Sponsor correspondence
- Training documentation

6. PROTOCOL IMPLEMENTATION

6.1 Informed Consent

The patient, guardian, or authorized agent(s) must provide written informed consent prior to undergoing any study procedures for the study. The Informed Consent Form (ICF) must have documented current IRB approval. All applicable signatures and dates should be completed on the ICF at the time of consent.

In addition, if the protocol is amended during the course of the study, the patient will be informed of any changes and the ICF will be updated to reflect the amended protocol. If required by your local IRB, active patients will need to sign a revised ICF.

If a patient turns 18 while active in the study, they will be re-consented as an adult patient.

6.4 ULTRASOUND DIAGNOSIS –suggested guidelines

6.4.1 Suggested diagnostic guidelines:

Compression is key to the diagnostic performance of ultrasound for deep vein thrombosis (DVT) diagnosis. Diagnosis and adjudication is optimal when the images taken by ultrasound capture each compression maneuver (i.e. on each segment of vein being interrogated), and do so as dynamic (i.e., few second video clip or “cine-file”, also known as AVI file on many machines) rather than as static images. This allows the radiologist to see whether (and to what extent) the walls of the vein appose during the compression maneuver—a key criterion for DVT diagnosis. The radiology report should clearly state the extent of the thrombus for each segment of the involved vessels including if there is complete occlusion or blood flow seen.

6.4.2 Suggested DVT diagnostic imaging protocol

Lower Extremity Venous Doppler – Bilateral, Right or Left

Scan patient with the highest frequency linear transducer available, usually 5 or 7.5 MHz. Each venous level should be documented by cine-clip as well as still images.

- Take representative compression pictures in transverse of each vein segment, using dual screen technique: show vein as is on the screen at left, with compression on the screen at right.
    - CFV, CFV and GSV, FV and PFV, FV, FV in Hunter’s canal if possible, popliteal vein.
    - Take one cine-clip of each compression maneuver (i.e., each vein segment interrogated).
    - Image calf veins if patient’s complaint is below the knee.
- Take representative color Doppler and spectral Doppler images of vein segments in longitudinal.
    - CFV, CFV and GSV, FV and PFV, FV, FV in Hunter’s canal if possible, popliteal vein.
    - Correct color orientation to make vein blue.
    - Augment only if there is no evidence for DVT using distal augmentation. DO NOT augment if clot is present.
- Position patient slightly sitting, about a 30º angle to demonstrate phasic flow.
- If thrombus is found, document extent of thrombus

Upper Extremity Venous Doppler – Bilateral, Right or Left

- IJV: dual screen compression, long grayscale, color and spectral waveform
- Innominate: long grayscale, color and spectral waveform
    - Best seen with transducer in transverse approach angled under the clavicle
- SCV: long grayscale, color and spectral waveform, for both segments supra/ infraclavicular
- Axillary: long grayscale, color and spectral waveform, dual screen compression
    - The axillary vein is distal to the first rib
- Basilic, brachialis, cephalic: dual screen compression, trans color
- Positioning:

    - For upper vessels: arm bent at 90º with hand across abdomen reduces compression of the SCV
    - Lower vessels: palm up, arm abducted out resting on scanner's knee
    - Cephalic vein: palm down, use very light pressure on anterior upper arm
- Limited Arm: if complaint is above clavicle and no DVT is seen in large vessels
    - If DVT is detected, follow into smaller vessels in distal arm
- Take representative compression pictures (in transverse of each vein segment, when possible) using dual screen technique: show vein as is on the screen at left, with compression on the screen at right.
    - Take one cine-clip of each compression maneuver (i.e., each vein segment interrogated).

7. DATA MANAGEMENT

9.1 Data Collection Methods

9.1.1 Source Documents

The study coordinating center has provided some documents that can be used as source documents including: the telephone questionnaire and PTS assessment. (see appendices). These forms do not imply that further information should not be added. During each patient visit, progress notes should be written in the patient's chart to document all procedures and/or significant observations.

9.1.2 Study Case Report Forms

All data will be entered into the EDC system, REDCap.
All data should be entered into the EDC within 5 days of the study visit.

9.2 Data Completion Instructions

CRF	Registration	2-year follow-up visit	Treatment	Outcomes	Deviation	Off Study
Registration	x					
Follow-up Visit		x				
Anticoagulant Treatment			x			
Antiplatelet Treatment			x			
Graduated Compression Stockings			x			
Recurrent Thrombosis				x		
Bleeding Event				x		
Protocol Deviation Summary					x	
Study Completion / Termination						x

9.3 Long Term Storage of the Source Documents

All study documents should be stored according to the clinical trial agreement or the site standard operating procedure (SOP) for storage of research studies upon study closure, whichever is longer.

9.4 Maintaining Data Privacy

Every attempt should be made to keep study documents private and secure. Sites should store all study documents in a place accessed only by relevant study personnel, accessible only by key or combination entry.

10. STUDY COMPLETION AND CLOSE-OUT PROCEDURES

Study close-out activities will be performed to confirm that the site investigator's study obligations have been met and post-study obligations are understood. Such close-out activities include, but are not limited to:

- Verification that study procedures have been completed, data collected, and study supplies have been returned to the responsible party or prepared for destruction (according to site SOP)
- Review of investigator's correspondence and study files against the coordinating center's records for completeness
- Assurance that all data queries have been completed
- Assurance that correspondence and study files are accessible for external audit

- Reminder to investigators of the ongoing responsibility to maintain study records and to report any relevant study information to the PM
- Ensure site investigator is aware of regulatory obligations and requirements for record retention
- Assurance that the investigator notifies the IRB after data clean up is finished and the PMs or DCC notify the site of study completion. A copy of the IRB notification is obtained.

APPENDIX E: Kids-DOTT Trial Telephone Questionnaire – Long Range Data Collection

(Performed at 2 years post diagnosis only if the site has been unsuccessful in getting the participant to return for an in-person follow up visit.)

Participant ID: _____ Date completed: _____

For ALL patients: Clinically Relevant Bleed Record

Have you experienced any bleeding episodes? Yes or NO

If YES, did you seek medical attention for the bleed (urgent care, Emergency Dept, unscheduled Primary Care Provider visit): Yes NO

Bleed details (if medical attention sought):

NOTE: Please complete Clinically Relevant Bleeding Events Summary eCRF for all bleeding episodes for which medical attention was sought.

Specific Patient Questions: Recurrent VTE Record

For patients with venous thrombosis involving the lower extremities and/or inferior vena cava (circle YES or NO):

Have you experienced any new or increased leg pain?	Yes or NO
Have you experienced any new or increased leg swelling?	Yes or NO
Have you experienced any new or increased shortness of breath?	Yes or NO
Have you experienced any new or increased chest pain?	Yes or NO

For patients with venous thrombosis involving the upper extremities, jugular vein, subclavian vein, brachiocephalic vein, and/or superior vena cava (circle Yes or NO):

Have you experienced any new or increased arm or neck pain?	Yes or NO
Have you experienced any new or increased arm or neck swelling?	Yes or NO
Have you experienced any new or increased swelling of the head or face?	Yes or NO
Have you experienced any new or increased shortness of breath?	Yes or NO
Have you experienced any new or increased chest pain?	Yes or NO

For patients with cerebral sinovenous thrombosis (circle Yes or NO):

Have you experienced any increase in severity of headache?	Yes or NO
Have you experienced any increased in the duration of headache?	Yes or NO
Have you experienced any new or increased blurred vision?	Yes or NO
Have you experienced any new or increased facial droop or facial weakness?	Yes or NO
Have you experienced any new or increased shortness of breath?	Yes or NO
Have you experienced any new or increased chest pain?	Yes or NO

For patients with renal vein thrombosis (circle Yes or NO):

Have you experienced any new or increased blood in the urine?	Yes or NO

Have you experienced any new or increased headache or blurred vision?	Yes or NO
Have you experienced any new or increased shortness of breath?	Yes or NO
Have you experienced any new or increased chest pain?	Yes or NO

For patients with hepatic or portal vein thrombosis (circle Yes or NO):

Have you experienced any increase in severity of abdominal pain?	Yes or NO
Have you experienced any new or increased shortness of breath?	Yes or NO
Have you experienced any new or increased chest pain?	Yes or NO

For patients with right atrium/right ventricle thrombosis (circle Yes or NO):

Have you experienced any new or increased shortness of breath?	Yes or NO
Have you experienced any new or increased chest pain?	Yes or NO

Have you been diagnosed with a recurrent clot in the past year?	Yes or NO

NOTE TO SITE: As part of best/standard clinical care, those patients answering yes to any of these questions should be clinically evaluated for possible thrombus progression, recurrent thrombosis, or thromboembolism, as appropriate. Note that as part of best/standard clinical care, similar questions to those contained in this telephone questionnaire should be addressed as part of the patient's interim history at each routine follow-up clinic visit.

_____ _____

Form Completed By **Date**

APPENDIX F: Kids-DOTT Trial Standardized Pediatric Post-Thrombotic Syndrome (PTS) Outcome Instrument (Manco-Johnson)

Participant ID: _____ Date of Birth: _____

Date of Clot Diagnosis: ___-___-_____ Date of Assessment: _____

Affected limb (circle): Arm □ Leg □

PHYSICAL FINDINGS (Signs)
Please measure to nearest tenth of one centimeter.

Limb Circumference Measurements	Right	Left
Mid-proximal limb	_____.___cm	_____.___cm
Mid-distal limb	_____.___cm	_____.___cm

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

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

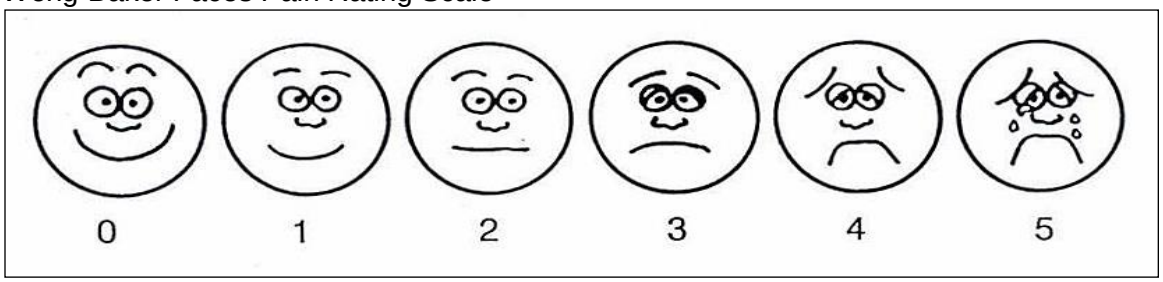
FUNCTIONAL FINDINGS (Pain Symptoms)
Wong-Baker Faces Pain Rating (Oucher) Scale: Score 0-5 for each.

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

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

Comments: _____

Wong-Baker Faces Pain Rating Scale



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

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

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

_____ _____

Form Completed By **Date**

APPENDIX K: Clinical Endpoint Adjudication Committee (CEAC) Submission Instructions

For the Kids-DOTT study when site staff become aware of a recurrent venous thromboembolism (VTE) or a clinically relevant bleed in a study subject, the following instructions should be followed for the timely and proper submission of documentation packets for CEAC review.

EVENT REPORTING WINDOWS:

Recurrent VTE: The start date of recurrent VTE (radiologic diagnosis date or symptom onset date) must be after the 6-week visit (window: 6 weeks -5/+7 days from date of radiologic diagnosis of index venous thrombotic event). The reporting window ends 2 years after the index venous thrombotic event or at study completion (2 year visit).

Clinically Relevant Bleed: The reporting window begins immediately following the date of radiologic diagnosis of the index venous thrombotic event. The reporting window ends 2 years after the index venous thrombotic event or at study completion (2 year visit).

Death: The reporting window begins immediately following randomization and ends at study completion (2 year visit).

EVENT REPORTING TIMELINES:
Study sites are responsible for timely and accurate reporting of any potential endpoint events identified for subjects enrolled at their study site. Any potential endpoint event must be reported through completion of the DATATRAK event-specific eCRF **within 2 business days** after the site staff learns of the event.

Endpoint Event	**Case Report Form (CRF)**
Recurrent VTE	Recurrent Thrombosis
Clinically Relevant Bleed	Clinically Relevant Bleeding Events Summary
Death	Study Completion / Termination
	Adverse Events Summary (if death occurs during AE reporting window)

COLLECTION OF SUBMISSION OF ENDPOINT EVENT SOURCE DOCUMENTS:
Each study site is responsible for collecting and preparing a complete set of source documentation for potential endpoint events that are identified (see list of documents below). To determine which source documents should be collected for a specific endpoint event, the study site should reference the table below. However, it is also critical for the study site to use their knowledge of the circumstances of the event to determine whether additional source documents – not included on the list – should also be provided.

All materials collected should be submitted to the site's Project Manager by email to and/or by mail to:

Johns Hopkins All Children's Hospital
600 5th Street South, Suite 3200
St. Petersburg, FL 33701

Endpoint Event Type	Expected Source Documentation (at minimum)
Recurrent VTE	• Hospital Admission History and Physical • Hospital Discharge Summary • Relevant Clinic Notes, Including Hematology Clinic Note (if no admission) • Radiologic Exam Report(s) • CD with Radiologic Images
Major or Clinically Relevant Non-Major Bleed	• Hospital Admission History and Physical • Hospital Discharge Summary • Transfusion Records • Hemoglobin & Hematocrit Laboratory Reports with Normal Reference Ranges • Relevant Clinic Notes, Including Hematology Clinic Note (if no admission) • Last Relevant Clinic Note *Prior* to the Date of the Event
Death	• Autopsy results (if available) • Death summary • Clinic or inpatient notes from the date of death as well as from at least two days prior to death (if clinic notes, clinic notes from the two outpatient visits preceding death) • Radiology reports and laboratory test results supporting the cause of death as ascribed by the PI