Prospective Multi-Center Evaluation of the Duration of Therapy for Thrombosis in Children
(the "Kids-DOTT" Trial)

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Project Title: Prospective Multi-Center Evaluation of the Duration of Therapy for Thrombosis in Children (the "Kids-DOTT" Trial)

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I. Hypotheses and Specific Aims/Purpose:

A. Statement of purpose

The main purpose of the Kids-DOTT trial is to provide key evidence for the optimal duration of anticoagulant therapy for venous thrombosis in patients <21 years old, given that the conventional duration of such therapy in children is derived solely from evidence in adult venous thromboembolism (VTE) trials. To fulfill this purpose, a multicenter randomized controlled trial (RCT) is necessary and herein described. Because of the large scope of this trial, an additional purpose during the vanguard study was to provide evidence of feasibility of the trial, via an initial internal/nested pilot/feasibility phase. Metrics were established during the vanguard study that would allow for advancement into the "rest of trial phase", for trial completion.

The Kids-DOTT trial specifically addresses the population of children with first-episode venous thrombosis in whom clinical characteristics do not indicate an *a priori* heightened risk for developing recurrent VTE or the post-thrombotic syndrome (PTS). As such, this trial adopts a rational, risk-stratified approach to antithrombotic therapy in children. In particular, it excludes those few patients in whom findings on initial diagnostic evaluation warrant a prolonged duration of anticoagulation (e.g., spontaneous/idiopathic event, prior VTE, underlying active cancer, severe hypercoagulable state), and then takes advantage of an additional clinical factor (early thrombus resolution/non-occlusion), in order to target a group of children who are most likely to realize a net benefit (from the risk/benefit perspective) of shortened-duration anticoagulation. Over 90% of VTE in children are classified as "provoked" (non-spontaneous), meaning that they have been provoked by the presence or insertion of a central venous catheter, recent hospitalization, surgery, trauma, immobility, infection, dehydration, flare of autoimmune condition, oral contraceptive use, etc. (see also Table 1 below).

The specific aims and corresponding hypotheses of the Kids-DOTT trial follow below.

B. Principal aims and hypotheses

Specific Aim #1: To evaluate the *efficacy* and *safety* of shortened-duration (6 weeks total) versus conventional-duration (3 months total) anticoagulation for first-episode, provoked, acute venous thrombosis among children in whom thrombus resolution/non-occlusion (i.e., blood flow) is evident after the initial 6 weeks of anticoagulant therapy.

> Hypothesis: Among children with first-episode, provoked, acute venous thrombosis in whom thrombosis is resolved or non-occlusive at six weeks follow-up, a shortened duration of anticoagulation (total six weeks; i.e. no further therapy) is non-inferior in efficacy to the conventional duration (total three months) of anticoagulation with respect to the risk of symptomatic recurrent VTE at 1 year, and is superior in safety with respect to the risk of clinically-relevant bleeding at 1 year. (The hypothesis will also be tested in secondary analysis at 2 years, using the same efficacy and safety outcomes as for the 1 year primary analysis.)

Specific Aim #2: To compare the composite efficacy of shortened-duration (6 weeks total) versus conventional-duration (3 months total) anticoagulation for first-episode, provoked, acute venous thrombosis among children in whom thrombus resolution/non-occlusion (i.e., blood flow) is evident after the initial 6 weeks of anticoagulant therapy.

> Hypothesis: Among children with first-episode, provoked, acute venous thrombosis in whom thrombosis is resolved or non-occlusive at six weeks follow-up, a shortened duration of anticoagulation (total six weeks; i.e. no further therapy) is non-inferior to the conventional duration (total three months) of anticoagulation with respect to a composite efficacy endpoint comprised of the 1-year risk of symptomatic recurrent VTE or PTS. (The hypothesis will also be tested in secondary analysis at 2 years.)

Specific Aim #3: To determine whether outcomes of first-episode, provoked, acute venous thrombosis (specifically, with respect to recurrent VTE and PTS) among children treated with conventional-duration (3 months total) anticoagulation differ between those with and without thrombus resolution/non-occlusion at 6 weeks.

Hypothesis: Among children with first-episode, provoked, acute venous thrombosis treated with conventional-duration (3 months total) anticoagulation, the cumulative incidences of recurrent VTE and PTS are significantly lower among those in whom thrombus was resolved or not completely occlusive (i.e., some blood flow observed) versus completely occlusive (no blood flow observed) after the initial 6 weeks of anticoagulant therapy.

Specific Aim #4: To establish a clinical trial-derived plasma and nucleic acids biorepository for future "omics" (e.g., proteomic, genomic, metabolomic) investigations of predictors and modulators of VTE outcomes in children.

Specific Aim #5: To investigate whether duration of anticoagulation (over the range of 3 months to indefinite duration, as determined clinically in routine care) on influences the risks of symptomatic recurrent VTE and clinically-relevant bleeding among children with first-episode, provoked, acute venous thrombosis in whom persistent antiphospholipid antibody (APA) positivity is evident at 6- and 12-weeks post-diagnosis.

Hypothesis: Among children with first-episode, provoked, acute venous thrombosis in whom persistent APA positivity is evident at 6- and 12-weeks post-diagnosis, duration of anticoagulant therapy is not a predictor of symptomatic recurrent VTE but is directly related to the risk of clinically-relevant bleeding.

Specific Aim #6 (exploratory): To evaluate whether the effect of treatment duration on the risks of symptomatic recurrent VTE and clinically-relevant bleeding in children with first-episode, provoked, acute venous thrombosis differs substantively between subgroups defined by type of sub-acute anticoagulant therapy in real-world clinical use (all prescribed clinically, with the exception of investigational dalteparin, which was prescribed under an investigator-held Investigational New Drug [IND] through December 2013).

For the internal/nested pilot/feasibility study completed during the vanguard phase of the trial, the specific aims were as follow:

(1) To provide pilot data on the proportion of children studied with acute thrombosis who exhibit thrombus resolution/non-occlusion (i.e., established blood flow) following 6 weeks of standard anticoagulant therapy, the occurrence of recurrent VTE and PTS in children studied, and the frequency of study drop-out;

(2) To evaluate the feasibility of web-based enrollment, randomization, and data collection over a 2-year follow-up period among participating sites;

(3) To determine the concordance (measured as percent agreement and κ) in the finding of completely occlusive thrombosis at the 6 week repeat imaging study (i.e., principal randomization criterion) for the reading by the blinded central adjudicating radiologist in comparison to the local clinical radiology report.

II. Background and Significance:

The problem of pediatric VTE has become increasingly apparent in recent years with advancements in diagnostic modalities for thrombosis, the rise in intensive approaches toward the support of critically ill children, and the heightened survival of children with chronic illnesses. VTE is one of the most frequent complications in children treated for major illnesses. Table 1 below illustrates common clinical risk factors for provoked venous thrombosis in children. In addition to those listed, a family history of VTE also serves as an important risk factor for VTE in children, but is not a sufficient criterion for provoked venous thrombosis (Goldenberg & Bernard, 2008).

Table 1. Examples of Common Clinical Risk Factors for VTE in Children (i.e., Provoked VTE)
Immobility or prolonged recumbency
Pregnancy/birth
Post-operative state
Trauma
Infection
Indwelling central venous catheter
Cancer
Glucocorticoid use
Estrogen use (e.g., oral contraceptives)
Dehydration
Chronic inflammatory condition (e.g., lupus, inflammatory bowel disease)
Ongoing/recent hospitalization

In both children and adults, the current standard of care is for anticoagulation of 3 months duration for a first-episode VTE in individuals with few and/or transient pro-thrombotic risk factors, based upon adult trials (Monagle et al., 2008, 2012). In the standard care of pediatric VTE patients, the degree of residual thrombus does not determine the duration of therapy and has not been shown to increase the risk of recurrent VTE. Rather, duration of therapy is guided in standard care by the chronicity of prothrombotic risk, as assessed by clinical and laboratory factors. A prolonged duration of anticoagulation (i.e., 6 months or longer, as opposed to 3 months) is indicated in VTE patients with chronic potent prothrombotic conditions and in those with unprovoked events (i.e., spontaneous; no clinical risk factors identified), given an increased risk of recurrent VTE in these groups (Monagle et al., 2008, 2012). Whether duration of anticoagulation in this group influences the risk of PTS is unknown.

A prolonged duration of anticoagulation is considered in APA syndrome, defined as the persistence of APA positivity 12 weeks following initial assessment following a thrombotic event. Given the lack of prospective data evaluating influence of duration of therapy on outcomes, past American College of Chest Physicians guidelines in 2008 (Monagle et al., 2008) recommended a broad range of duration of anticoagulation in APA syndrome, from 3 months to life-long; in 2012, these guidelines did not directly address the issue (Monagle et al., 2012). Hence, available guidelines are of limited help in guiding decisions by physicians and their patients regarding anticoagulant therapy duration in pediatric APA syndrome, and rigorously-collected prospective observational data in pediatric APA syndrome are urgently needed.

All anticoagulants used in the standard of care for pediatric VTE treatment are prescribed without a formal Food and Drug Administration (FDA)-approved indication for same (with the exception of intravenous direct thrombin inhibitors approved for use specifically in thrombosis related to heparin-induced thrombocytopenia [HIT] syndrome). Nevertheless, information on dosing in children is provided in the labeling of several anticoagulant agents (e.g., unfractionated heparin; low molecular weight heparins [LMWH]; warfarin; argatroban; fondaparinux). In both children and adults, either unfractionated heparin or LMWH may be used during the initial (i.e., acute) therapy phase, while either LMWH or warfarin may be used during the subsequent (i.e., subacute) therapy phase.

Because there has been no clear evidence that, among the aforementioned anticoagulants presently used in standard care, a particular agent/regimen has a distinct risk of recurrent venous thromboembolism (Monagle et al., 2008, Buller et al., 2004), adult trials of duration of anticoagulant therapy for VTE--which have been performed over the past two decades in multiple settings--have not been restricted to a particular anticoagulant agent/regimen (Campbell et al., 2007; Agnelli et al., 2001; Pinede et al., 2001; Schulman et al., 1997; Schulman et al., 1995). Among these, several studies performed in the 1970s and 1980s evaluated shortened-duration anticoagulation therapy (ranging from 3 to 6 weeks) in adults with first-episode VTE, the findings of which suggested that shorter therapy was not associated with increased risk

of recurrence. However, the validity of the latter studies has been questioned by others who subsequently demonstrated an 8.6% increase (from 9.5% to 18.1%) in the risk of recurrent VTE at 2 years among patients treated for 6 weeks as compared to 6 months (Schulman et al., 1995). Yet in children, prospective studies of patients treated for first-episode VTE suggests that the incidence of recurrent VTE in the pediatric population may be much lower than that in adults, at only 7-11% at 2 years, leading some authors to conclude that "...optimal treatment and long-term outcome of pediatric symptomatic and asymptomatic VTE need to be studied" (van Ommen et al., 2001).

Studies to shorten the duration of anticoagulant therapy for thrombosis have in the past been undertaken largely because of the need for frequent invasive monitoring by venipuncture in patients treated with warfarin, and the risk of bleeding in such individuals. Bleeding is estimated to occur in 20% of children treated with therapeutic doses of oral anticoagulants, with a rate major/clinically-significant hemorrhage of nearly 2% per year (Monagle et al., 2008). In patients treated with LMWH as the subacute anticoagulant, efforts to shorten the duration of therapy are prompted by concerns of the invasiveness of twice-daily subcutaneous injection necessitated by this form of treatment, its considerable expense, the as yet unclear risk of osteoporosis relative to that found with unfractionated heparin, and bleeding risks. Preliminary experience with a therapeutic course of LMWH in children suggests an overall bleeding rate of 17%, and a rate of major hemorrhage of 4% (Monagle et al., 2008). Nevertheless, the desire to decrease cost and bleeding risks by shortening the duration of anticoagulant therapy must be balanced by the need to minimize risk of recurrent thrombosis. Unfortunately, the relative risk of recurrent VTE for shortened anticoagulation in the pediatric setting is unknown. Since the rate of recurrent VTE in children treated with standard duration anticoagulation appears to be quite lower than that for adults treated similarly, it is expected that the absolute increase in risk of recurrent VTE (if any) engendered by shortened anticoagulation will be smaller than that in adults. It is interesting to also consider that many experts in the field believe that the rate of recurrent VTE is highest among patients with unprovoked/idiopathic VTE, and that in such patients, this risk may be constant following cessation of therapeutic anticoagulation, regardless of its duration.

No large prospective, randomized, controlled trials on the optimal duration of anticoagulation for first-episode VTE have been performed to date in children. Pediatric guidelines recommending 3 months duration of anticoagulation for first-episode provoked VTE remain are largely based upon prospective adult data using recurrent VTE and mortality as primary endpoints (without consideration of functional status, as would be reflected in an additional endpoint of PTS). Yet, PTS is believed to occur in approximately 26% of pediatric and adult patients, following limb deep vein thrombosis (DVT) (Goldenberg, 2010a). as the authors of these recommendations have noted in the past, there is urgent need to "convince both peer review agencies and pharmaceutical companies that pediatric trials require a specific dedicated approach." The Kids-DOTT trial responds to this urgent need, establishing a large multinational collaborative network of academic centers to investigate duration of anticoagulation for provoked venous thrombosis in patients <21 years of age, via an NIH-defined phase 3 RCT.

III. Preliminary Studies/Progress Report:

Apart from the vanguard phase (nested pilot/feasibility study) of the Kids-DOTT trial, we are not aware of any prior or preliminary studies stratifying duration of anticoagulant therapy for VTE according to the presence of absence of residual occlusive thrombosis after 6 weeks of initial anticoagulant therapy. Prior studies that have evaluated short-duration anticoagulation in adult VTE (notably, not limited to or stratified upon early thrombus resolution/non-occlusion) have been cited above (see Background and Significance).

The vanguard phase (nested pilot/feasibility study) of the Kids-DOTT trial was published in 2015, and provided blinded aggregated (full RCT population) outcomes data on the primary efficacy and safety endpoints for Kids-DOTT, by which to refine the final sample size for the rest-of-trial phase (Goldenberg et al., 2015). The vanguard phase also demonstrated the feasibility of multicenter accrual and the fidelity of randomization, including a high reliability of locally-determined presence/absence of completely occlusive DVT as the key radiologic criterion for randomization.

IV. Research Methods: Summary of Study Rationale

A. Primary Outcome(s):

PRIMARY EFFICACY: Occurrence of symptomatic recurrent VTE within 1 year

PRIMARY SAFETY: Occurrence of clinically-relevant (i.e., major plus clinically-relevant non-major [CRNM]) bleeding within 1 year.

Based upon International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee standardized definitions for pediatric trials (Mitchell et al., 2011), "Major bleeding" will be characterized by bleeding satisfying any one of the following criteria: 1) fatal; 2) clinically overt and associated with a decrease in hemoglobin of at least 2 g/dL in a 24 hour period; 3) clinically overt and for which blood product is administered; 4) retroperitoneal, pulmonary, or involving the central nervous system; 5) requiring surgical intervention in an operating suite.

"CRNM bleeding" definition includes any bleeding that does not fulfill the above criteria but fulfills one of the following: 1) Bleeding requiring medical or surgical intervention to restore hemostasis; 2) Bleeding for which medical attention is sought.

B. Secondary Outcome(s):

SECONDARY EFFICACY:

1) Occurrence of symptomatic recurrent VTE or development of PTS (composite endpoint) within 1 year;
2) Occurrence of symptomatic recurrent VTE within 2 years;
3) Development of PTS within 1 year;
4) Development of PTS within 2 years.

C. Endpoint Adjudication:

Primary efficacy and safety outcomes, as well as all death events, will be centrally adjudicated via an independent, blinded Clinical Endpoint Adjudication Committee (CEAC), using a standardized process delineated in the CEAC charter. The history and physical exam findings from clinical encounters corresponding to primary outcome events (recurrent VTE and clinically-relevant bleeds) will be reviewed by the clinical experts on the committee. In addition, for VTE, clinically-relevant bleeding and death events, relevant imaging studies (as applicable) will be reviewed by a central adjudicating radiologist on the committee.

D. Summary of Research Methods and Study Design:

The present proposal is for a definitive RCT powered to evaluate non-inferiority of shortened-duration (6 weeks) versus conventional-duration (3 months) anticoagulation in children with first-episode, provoked, acute venous thrombosis. The design of the Kids-DOTT trial has been published (Goldenberg et al, 2010b), and follows that of a prospective randomized open-label blinded-endpoint (PROBE) design, wherein treatment is non-blinded but outcome assessment is blinded. Furthermore, the Kids-DOTT trial employs a parallel-cohort RCT design, which in the setting of a rare disease affords not only the testing of the primary hypothesis, but also generation of key natural history data and event rates to inform the design of future trials addressing the disease population not represented by the randomized study population.

The trial is conducted in two phases, with the first phase being a pilot/feasibility study with scheduled pilot analysis (to validate target sample size, among other pilot/feasibility metrics) after the first 100 enrolled patients, and the second phase being the completion of the definitively powered trial. The former phase was completed in 2015 and the latter phase is ongoing.

The Clinical Coordinating Center (CCC) is at Johns Hopkins University and the Johns Hopkins All Children's Hospital (JHACH; St. Petersburg, FL). The Data Coordinating Center (DCC) is at both CPC Clinical Research (CPC; Aurora, CO), an Academic Research Organization affiliated with the University of Colorado and Johns Hopkins All Children's (St. Petersburg, FL). The NIH U01-specified aims, including all randomized controlled trial (RCT) analyses, are handled by the DCC at the University of Colorado. The Publications Committee and Steering Committee (with representation from NIH) have approved a plan for multiple secondary analyses (observational, non-RCT) that will involve the University of Colorado DCC, the JHACH DCC for Pediatric Multicenter Studies, or both. The currently envisioned secondary manuscripts approved by the Publications Committee and Steering Committee are shown in Appendix 2: Publication Plan, along with the DCC taking primary responsibility for the analysis.

Coordinating center personnel have extensive experience in the conduct of numerous large collaborative trials, including pediatric trials. In addition to routine DCC functions, CPC provides (or has provided) additional assistance with trial oversight, including: safety monitoring/pharmacovigilance (Medical Safety Officer) and serious adverse event (SAE) reporting to FDA; Data and Safety Monitoring Board (DSMB) report preparation; Steering Committee management; and Clinical Endpoint Adjudication Committee management. CCC and DCC key personnel include:

Overall (global) Principal Investigator:	Neil Goldenberg, MD, PhD (JHU)
Steering Committee Chair:	Sam Schulman, MD (McMaster)
Central Adjudication Ctte Chair:	Donald Yee, MD (Baylor Univ.)
Multi-Site Project Managers:	Frances Hamblin, RN (JHACH) Laurel McDevitt (JHACH)
Lead Biostatistician(s):	John Kittelson, PhD (Univ of Colorado) Ernest Amankwah, PhD (JHACH)
Biorepository Manager:	Billy Schleif, MS, MT (AAB) (JHACH)

As noted above, the primary question in Kids-DOTT is duration of anticoagulant therapy, and is not specific to (a) particular anticoagulant agent(s). The study is designed to maximize generalizability to future practice; therefore, anticoagulant regimen is not determined by the study, but rather is "observed" and tracked as part of the study, with subgroup analyses (based on anticoagulant regimen) planned as part of the analyses (within the limitations of statistical power achieved). Accordingly, at the time of enrollment, children with acute venous thrombosis who meet eligibility criteria will have already undergone prescription and selection of anticoagulant under the direction of their treating clinician in accordance with standard clinical care. Anticoagulant intensity will be monitored in accordance with best/standard clinical care and maintained within therapeutic goals established by current guidelines for anticoagulant therapy in children. Anticoagulation will be standard of care and therefore will not be provided as part of the study.

The current guidelines for anticoagulant therapy in children with first-episode acute venous thrombosis in children (which have not substantively changed since 2004) are as follows (adapted from Monagle et al., *Chest* 2012):

Initial (Acute) Therapy

LMWH by subcutaneous injection every 12h to achieve an anti-Xa activity level of 0.5-1.0 U/mL (alternatively, 0.5-1.2 U/mL)

OR

Unfractionated heparin by continuous intravenous infusion to achieve an anti-Xa level of 0.35-0.7 U/mL

Subsequent (Sub-acute) Therapy

LMWH by subcutaneous injection every 12h to maintain an anti-Xa level of 0.5-1.0 U/mL (alternatively, 0.5-1.2 U/mL)

OR

Vitamin K antagonist (e.g. warfarin)* orally once-daily to maintain an International Normalized Ratio (INR) of 2.0-3.0

* For oral vitamin K antagonist therapy, LMWH/unfractionated heparin is discontinued after approximately 7 days of LMWH/unfractionated heparin therapy, when the INR has been > 2.0 for 2 consecutive days.

None of the aforementioned standard anticoagulants is FDA- or European Medicines Agency (EMA)-approved for an indication of VTE treatment in children, and yet these agents are key components of the standard of care for VTE treatment world-wide (Goldenberg et al., 2015b). Children in the Kids-DOTT trial will be permitted to continue to receive the intravenous direct thrombin inhibitor bivalirudin in lieu of unfractionated heparin and will be permitted to use the synthetic pentasaccharide fondaparinux in lieu of low molecular weight heparin, when prescribed these agents clinically. As part of standard care for VTE treatment at a number of pediatric centers, bivalirudin is employed as an alternative to unfractionated heparin as the acute anticoagulant, and fondaparinux is employed as an alternative to LMWH as the subacute +/- acute anticoagulant.

Given recent FDA and EMA approvals of the oral direct anticoagulant agents dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) for the treatment of VTE in adults, and their emerging off-label use in pediatrics paralleling that of the aforementioned standard anticoagulants (Goldenberg et al., 2015b), children enrolled in the Kids-DOTT trial will be permitted to use the direct oral anticoagulants in lieu of warfarin, when prescribed these agents clinically or via concomitant enrollment in an investigational drug study (where permissible according to the latter protocol).

Patients with limb DVT may also be prescribed graduated compression stockings as part of their supportive care, in accordance with the local standard of care. (This prescription will be tracked in the study as a covariate.)

For those centers in whom laboratory thrombophilia testing is performed as part of routine clinical care in the target population, this will have been performed clinically by the time of enrollment; those centers in whom laboratory thrombophilia testing is not considered to be part of standard/best clinical care will perform this testing on patients who have provided informed consent for study participation and are undergoing screening procedures for the study.

The overall study schema, with regard to enrollment, randomization (versus observational parallel cohort assignment), and long-term follow-up, is shown below (Figure 1).

The study Schedule of Events is shown below (Table 2), followed by a more detailed description of the procedures and components that comprise each visit in Section E. All visits are timed from the date of radiologic diagnosis.

Table 2. Schedule of Events

Assessment Performed	Screening Visit 1	Clinic Follow-up Visit 2	Telephone Follow-up Visit 3	Clinic Follow-up Visit 4	Clinic Follow-up Visit 7[&] **	Clinic Follow-up Visit 8**	Clinic Follow-up Visit 9**
	Within 30 days diagnosis	6 weeks -5/+7 days post-diagnosis	8 weeks +/- 7 days post-diagnosis	12 weeks +/- 10 days post-diagnosis	6 months +/- 14 days post-diagnosis	1 year +/- 30 days post-diagnosis	2 years +/- 30 days post-diagnosis
Informed consent	X						
Enrollment	X[#]						
Full medical history	X	X		X	X	X	X
Physical exam	X	X		X	X	X	X
Height & Weight	X						
Thrombophilia Testing	X[a]	X[c]					
Research Blood		X[b]		X[b]			
Telephone questionnaire [d]			X		X**	X**	X**
Patient Diary and Anticoagulant Calendar Review		X	X	X			
Web-based data collection	X	X	X	X	X	X	X
Recurrent VTE history		X	X	X	X	X	X
Bleeding history		X	X	X	X	X	X
PTS evaluation^					X[%]	X[%]	X[%]
AEs assessment (for randomized participants only)		X	X	X			
Randomization		X[#]					

[a] Protein C; Protein S; Antithrombin; APA Testing:
Anticardiolipin Antibody (ACA) IgM, Beta-2 Glycoprotein IgG, Beta-2 Glycoprotein IgM; Lupus Anticoagulant (LAC) – only one of the following is required:
dRVVT, aPTT-based Hexagonal Phospholipid, or aPTT-based Non-hexagonal Phospholipid. Anticoagulant monitoring as appropriate, if not yet documented within the goal therapeutic range
[b] Research blood for CloFAL assay, plasma proteomics is required for all participants. Research Blood for DNA/RNA only collected for those participants who consent to genetic material). (See Lab Manual for details)
[c] Repeat testing of any APA testing that was positive at diagnosis or if not done at screening.
[d] Telephone questionnaire available in the Manual of Operations (MOO)

[&] The original protocol contained telephone visits for visits 5 and 6; current visit schedule has not been renumbered, so as to avoid inconsistency in visit numbering/tracking relative to prior protocol versions.
**The 6 month, 1 year, and 2 year visit may be conducted as a telephone visit if the site has been unsuccessful in getting the participant to return for an in-person follow-up visit (in which case the PTS assessment is not performed).
[#]Eligibility for enrollment must be confirmed by CCC prior to enrollment. Eligibility for randomization must be confirmed by CCC prior to randomization or assigning to parallel cohort. See MOO for additional details.
[%]PTS Assessment required if visit done in person.
^ Manco-Johnson Instrument; for participating sites (if applicable), may include Modified Villalta Scale in addition to Manco-Johnson Instrument

For all participants, additional pertinent clinical data will be captured as follows: nature of the initial venous thrombosis episode (with detail as to signs/symptoms, symptom onset, anatomic site, and veno-occlusion); results of coagulation and thrombophilia testing; antithrombotic agents employed (both acute and sub-acute) and their intensities (i.e., results of standard anticoagulant monitoring assays); lag time from symptom onset to achievement of therapeutic anticoagulant levels; veno-occlusion and thrombus resolution at 6 weeks; nature of any major or minor bleeding episodes (as defined in Section IV B, above) during the anticoagulant therapy period (with detail as to amount of any related blood transfusion and/or any anticoagulant reversal required—see also Data and Safety Monitoring Plan section); and nature of any recurrent VTE (with detail as to signs/symptoms, anatomic site, and veno-occlusion). Data collection case report forms (CRFs) and SAE report forms derived directly from the web-based electronic data capture system are provided in the MOO. All adverse events and anticoagulant adherence in a calendar (example supplied in the MOO) from time of enrollment through the end of the sub-acute anticoagulant treatment.

Children will complete their participation in the trial at the 2 years post-diagnosis end-of-study visit/phone call. However, all children who have had outcome visits will be retained in the primary analysis of recurrent VTE and PTS risk (see Data Analysis Plan, below). In addition, as noted previously, the primary efficacy and safety endpoint collection occurs at the 1 year follow-up visit.

E. Description of Population to be enrolled:

1. Target Enrollment

In order to achieve adequate power and precision for the non-inferiority decision in the primary analysis (see also section G, below), the target enrollment is 815 children, from among a total of approximately 50 participating sites. This target enrollment accounts for an estimated 15% randomization non-eligibility rate (i.e. parallel cohort assignment; Goldenberg et al., 2010a) and a 15% non-retention rate in the per-protocol population (see definition in section G, below). Both males and females of all races and ethnic groups are eligible for this study.

2. Inclusion Criteria

(1) Children (birth to <21 years of age) with radiologically-confirmed acute deep venous thrombosis in the past 30 days

(2) In the opinion of the investigator, the venous thrombosis was a provoked (i.e., non-spontaneous) event (e.g.: hospitalization; Central venous catheterization; infection; dehydration; surgery; trauma; immobility; use of estrogen-containing oral contraceptive pills; flare of autoimmune/rheumatologic condition).

3. Exclusion Criteria

(1) Prior episode of VTE
(2) Malignancy that, in the opinion of the treating oncologist, is not in remission (note: remission may exist on or off anti-neoplastic therapy)
(3) Systemic lupus erythematosus
(4) Pulmonary embolism that is not accompanied by DVT or is more proximal than segmental branches of the pulmonary artery
(5) Use of, or intent to use, thrombolytic therapy
(6) Chronic anticoagulant at *prophylactic dosing* is being or will be administered beyond 6 months post VTE diagnosis
(7) Moderate/severe anticoagulant deficiency (defined by any one of the following):
    a. protein C <20 IU/dL if patient is ≥3 months of age, or protein C below lower limit of detection if patient is <3 months of age;
    b. antithrombin <30 IU/dL if patient is ≥3 months of age, or antithrombin below lower limit of detection if patient is <3 months of age;
    c. protein S (free antigen or activity) <20 IU/dL.

NOTE regarding pregnancy and eligibility:
A patient who develops a DVT while pregnant who has no other provoking factor beyond the pregnancy will remain ineligible for this study.

F. Description and Justification of Procedures, Measures, and Data Collection Tools:

Except as noted above (i.e., at some participating centers in which thrombophilia testing employed in participant qualification for enrollment is not routinely performed as part of best/standard clinical care), the only laboratory assays, examinations, or other procedures performed solely for the purposes of this study and not currently part of best/standard clinical care are the additional 10 mL blood specimens (6 mL for infants) obtained at 6 weeks and 3 months for protocol-specified prognostic marker investigations and future unspecified research (i.e., biobanking, when permission given for the latter via opt-in during the informed consent process). These biospecimens will be stored in the Johns Hopkins All Children's Pediatric Biorepository at the Clinical Coordinating Center. All biospecimen storage tubes are pre-labeled with a unique 2D barcode, with the association between the barcode and the participant's unique study ID maintained in the Biorepository's secure, web-based, password-protected Lab Information Management System (LIMS) maintained behind the information technology firewall at Johns Hopkins All Children's Hospital. Biospecimens will be used to identify and validate putative prognostic biomarkers in pediatric venous thrombosis (predictors/modifiers of risk of outcomes – recurrent VTE, bleeding, PTS). The genetic investigations will involve candidate gene, a genome-wide association study (GWAS), and whole genome sequencing approaches in deoxyribonucleic acid, as well as confirmatory approaches in the transcriptome (mRNA). In addition, we will perform non-genetic "omics" investigations involving proteomics/peptidomics, metabolomics, and lipidomics (Goldenberg et al., 2014). The Johns Hopkins All Children's Pediatric Biorepository uses a secure database to store all data related to the samples, behind the institutional firewall. Following completion of the protocol-specified aims, external requests for specimens in the Kids-DOTT trial biobank will be vetted and made available through the National Institutes of Health (NIH), in accordance with NIH policies on data and biospecimen sharing. Throughout their study participation, up to and including visit 4, patients will be asked to record adverse events and medication adherence in a diary (See MOO).

Visit 1 – Within 30 days of radiologic diagnosis:

- Informed consent
- Full medical history and physical exam
- Thrombophilia testing:
    - Protein C level (activity preferred)
    - Protein S level (free protein S antigen preferred)
    - Antithrombin (III) level (activity preferred)
    - APAs (including lupus anticoagulant):
        - Anti-cardiolipin IgM
        - Beta-2 glycoprotein IgG
        - Beta-2 glycoprotein IgM
        - Lupus anticoagulant – testing paradigm must include both a mixing study and a phospholipid neutralization step, as per ISTH guidelines for lupus anticoagulant testing (note: if both steps are included in a single test, then that single test will suffice for lupus anticoagulant testing):
            - dilute Russell Viper Venom Time (dRVVT), AND/OR
            - aPTT-based Hexagonal Phospholipid (e.g., STA-Clot), AND/OR
            - aPTT-based Non-hexagonal Phospholipid (e.g., lupus-sensitive aPTT)

Visit 2 – 6 weeks (+7/-5 days) post-diagnosis:

- Full medical history* and physical exam
- Research blood collection (Please refer to laboratory manual for details)
- Repeat imaging, using the same imaging modality as was used for thrombosis diagnosis. This is part of best/standard clinical care at participating centers. Note: Repeat imaging at 6 weeks is not required if interim imaging was already performed clinically and showed complete resolution of thrombosis.
- Repeat testing of any APA tests that were positive at enrollment (see Visit 1 for details). As described above for thrombophilia testing at enrollment, this repeat APA testing is performed as part of best/standard clinical care at many but not all participating centers. Note: Positive APA is defined as any of the following or combination thereof:
    - Anticardiolipin (IgM) >20 MPL U/mL
    - Beta-2 Glycoprotein (IgG) >20 GPL U/mL
    - Beta-2 Glycoprotein (IgM) >20 MPL U/mL
    - dRVVT abnormal/positive
    - aPTT-based, Hexagonal Phospholipid abnormal/positive
    - aPTT-based, Non-Hexagonal Phospholipid abnormal/positive
- Randomization vs. non-random assignment to an observational arm ("parallel cohort"; Goldenberg et al. 2010a)
    - Participants with evidence of complete resolution of deep venous thrombosis, residual non-occlusive thrombus in a non-distal deep venous system, or residual occlusive thrombus confined to a distal venous system (constituting the "thrombus resolution/non-proximal-

occlusion group"), AND who do not have persistent APA, will be randomized to receive one of two anticoagulant treatment durations:

- total duration of 6 weeks (shortened-duration arm; no further anticoagulation)
  - Participants who are randomized to 6 weeks of treatment will be instructed to stop anticoagulation after completing a minimum of 42 days of anticoagulant therapy
- total duration of 3 months (conventional duration arm)

Randomization will be stratified by age group (neonate; non-neonatal, non-teen child; teen); and thrombus location group (lower extremity DVT; upper extremity DVT; cerebral sinovenous thrombosis; all other).

- Participants with evidence of residual completely-occlusive, non-distal deep venous thrombosis (absence of flow through an entire venous segment will not be randomized, and instead constitute a "parallel cohort" (observational group) for "completely-occlusive non-distal deep venous thrombosis". Participants in this parallel cohort will be non-randomly assigned a total duration of 3 months of anticoagulant therapy and followed in the study with the same visit schedule as occurs for participants in the randomized arms.
- Children whose APA testing is still positive will not be randomized, and instead constitute a second parallel cohort (observational group) for "persistent APA". Participants in this arm will be non-randomly assigned a total duration of anticoagulation of at least 3 months, with exact duration as per physician discretion. Given that these patients may be clinically diagnosed with APA Syndrome in further follow-up at 3 months (as per ISTH criteria), prolonged anticoagulation may be clinically prescribed; exact duration of therapy will be observed and recorded for the purposes of the non-primary aims of the study. Participants in this parallel cohort will be followed in the study with the same visit schedule as occurs for participants in the randomized arms.

Visit 3 – 8 weeks (+/- 7 days) post-diagnosis Telephone Follow-up:

- Brief scripted telephone assessment of symptoms of concern for bleeding events and possible recurrent VTE. Please refer to MOO for the Telephone Questionnaire Form.

Visit 4 – 12 weeks (+/- 10 days) post-diagnosis:

- Interim history* and physical examination
- Research blood collection (Please refer to laboratory manual for details)

Visits 5 & 6:

No longer required beyond the vanguard phase of the trial (as of Protocol Version 9/15/2016) but numbering remains the same for consistency between protocol version.

Visit 7 – 6 months (+/- 14 days) post-diagnosis:

- Interim history* and physical examination
- PTS evaluation. This is part of best/standard clinical care at participating centers. (Please refer to MOO for the Manco-Johnson Instrument and the Modified Villalta Score. The research will primarily record the former, while the latter will be recorded on an optional basis in support of non-primary analyses.) Note: PTS examiners will be blinded to treatment duration as well as to affected limb.

- If the visit cannot be conducted in-person, the history and physical as well as the PTS evaluation will not be completed. Instead please refer to the Telephone Questionnaire – Long Range Data Collection Form in the MOO.

Visit 8 – 1 year (+/- 30 days) post-diagnosis:

Follow-up clinic visit assessments will include:

- Interim history* and physical examination
- PTS evaluation. (Please refer to details provided for visit 7.)
- If the visit cannot be conducted in-person, the history and physical as well as the PTS evaluation will not be completed. Instead please refer to the Telephone Questionnaire – Long Range Data Collection Form in the MOO.

Visit 9 – 2 years (+/- 30 days) post-diagnosis:

Follow-up clinic visit assessments will include:

- Interim history* and physical examination

PTS evaluation. (Please refer to details provided for visit 7). If the visit cannot be conducted in-person, the history and physical as well as the PTS evaluation will not be completed. Instead please refer to the Telephone Questionnaire – Long Range Data Collection Form in the MOO.

*For visits 2-9, report of interim history of clinically relevant bleeding episodes (see outcome definition, above) or recurrent VTE, if not presenting to the participating site principal investigator as treating hematologist, will be verified by clinical documentation obtained from corresponding medical records. Additional clinical evaluations prompted by a clinical suspicion of recurrent VTE shall be performed at the discretion of the treating clinician; however, information from these visits regarding signs/symptoms and imaging findings will also be captured for study analysis. The treating hematologist will remain responsible for overseeing the management of bleeding and recurrent VTE episodes.

Pregnancy during study participation:

A participant who has completed anticoagulant treatment for DVT and then becomes pregnant can remain enrolled on study for long-term follow-up purposes.

A participant who is still on anticoagulant treatment when she becomes pregnant, may be retained in the study on the allocated treatment duration arm so long as the primary hematologist believes that this is clinically appropriate; else she will be withdrawn from the study and treated with the clinically-indicated duration of anticoagulation.

Off-Study Criteria:

1. Participant not randomized within 8 weeks of radiologic diagnosis of qualifying VTE, despite meeting criteria for randomization.
2. In the investigator's opinion, it is in the participant's best interest to discontinue participation.
3. Study discontinuation by sponsor, IRB, or other regulatory body.
4. Lost to follow-up: Participants will not be deemed lost to follow-up until they have had no successful contact by the end of the 2 year visit window. Sites must document all attempts to contact the participant.
5. Participant stops anticoagulation prior to randomization and does not intend to continue further anticoagulation.

G. Potential Scientific Problems:

Although this study involves relatively minimal intervention, main potential problems and challenges include loss to follow-up/drop-out during the follow-up period, low endpoint rates, and the rather large projected number of patients required to achieve adequate power. These challenges were indeed observed during the pre-specified pilot/feasibility period of the study. The Steering Committee recommended strategies to overcome these challenges, and these recommendations were adopted and reflected via protocol modifications during the pilot/feasibility period and the transition from the vanguard phase to the NHLBI U01-funded phase of the trial.

Other challenges stem from the multi-center nature of the study, including uniformity of data collection and anticoagulant management, and timely data entry into the EDC system. These challenges are overcome via the CCC and DCC structure and close oversight of the trial, the use of EDC system with standardized eCRFs, and the agreement of all participating centers to follow established anticoagulant management guidelines (American College of Chest Physicians) for pediatric VTE treatment. During the pilot/feasibility period of the trial, these potential challenges did not materialize as substantive issues.

H. Data Analysis Plan:

The statistical analysis plan was developed by John Kittelson, PhD, biostatistician expert on the trial's Steering Committee, and Lead Biostatistician at the DCC. The primary hypothesis concerns non-inferiority of shortened-duration when compared with conventional duration anticoagulation therapy. In accordance with the convention for non-inferiority trials, the primary analysis is per-protocol (PP) for the primary endpoint. Analytic populations will be defined as follows:

a) Intent-to-treat (ITT): All randomized patients (i.e., excluding those in the parallel cohorts), analyzed according to randomization assignment.

b) Per-protocol: All randomized patients (i.e., excluding those in the parallel cohorts) who: completed follow-up through at least the 6 month visit; received 80% and 120% of doses of anticoagulant medication based on protocol-prescribed randomized duration of anticoagulation; AND had no protocol violations in eligibility criteria.

c) Safety: All randomized patients who have received at least 1 dose of anticoagulant post-enrollment.

The original design of the Kids-DOTT trial was based on historical observational studies which report a 10% annual rate of recurrent VTE and a 10% annual rate of clinically relevant bleeding. In the first half of the trial the risk has been much lower than the original design assumptions; that is, the observed risk is about 3% for recurrent VTE and about 1% for the bleeding endpoint. The updated Kids-DOTT statistical analysis plan describes how the bivariate decision curve will be revised when the recurrent VTE and bleeding risks differ from the pre-trial estimates. The analysis plan does not include an interim analysis because the reduced risk for the VTE and bleeding endpoints does not provide sufficient information to support an interim analysis prior to trial completion.

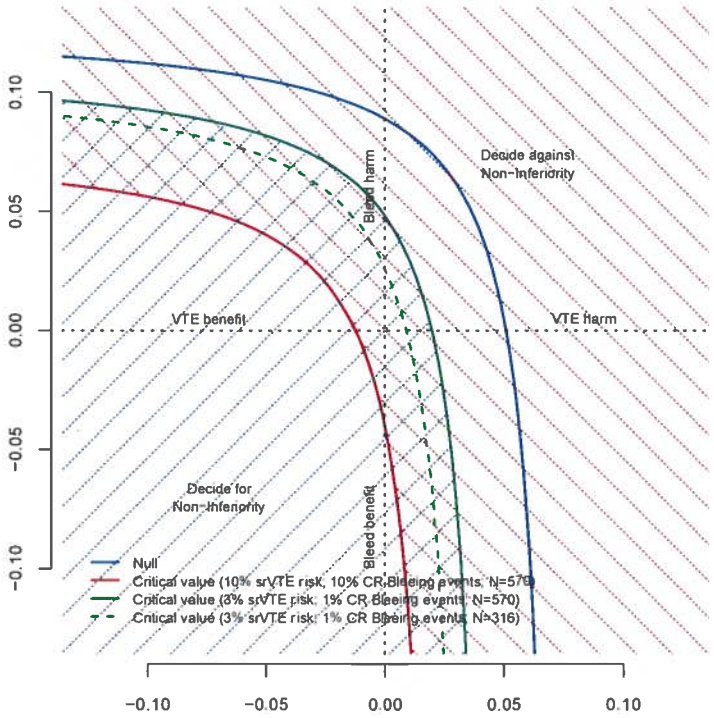
It is important to recognize that no relevant placebo-controlled RCT data exist by which to understand the effect size of anticoagulant therapy, and hence to inform the statistical calculation of a non-inferiority margin in this manner. Therefore, the non-inferiority margin has been set by clinical consensus among the participating investigators and with the approval of the Steering Committee, as an absolute increase of <6% in the risk of recurrent VTE at one year for the shortened-duration arm relative to the conventional-duration arm. Statistical methods for sample size estimation have then employed this margin as the upper bound of the 95% confidence interval. Therefore, upon trial completion we will conclude non-inferiority if the upper limit of the final 95% confidence interval rules out an absolute increase in symptomatic recurrent VTE of 6% or larger. When the upper bound of the 95% confidence interval is less than 6%, the **observed absolute increase in symptomatic recurrent VTE will be <1%**. The acceptability of this non-inferiority margin on the primary efficacy endpoint is based on a simultaneous presumption of reduction in risk of clinically-

relevant bleeding (i.e. bivariate endpoint approach)—specifically, a **hypothesized absolute risk reduction in clinically-relevant bleeding of ≥5%**—as further detailed below.

Given that duration of anticoagulation in VTE reflects a balance between efficacy (symptomatic recurrent VTE) and safety (clinically-relevant bleeding) as defined in the Primary Outcome Measures section above and given the hypothesis that bleeding will be reduced in children receiving shortened-duration anticoagulation, the statistical analysis will employ a bivariate endpoint analysis (i.e., trade-off approach). With a sample size of 285 per group in the randomized population, there is 82% power to conclude non-inferiority at an observed absolute increase in recurrent VTE of 1% (i.e., critical value of 1%, 95% CI upper bound of <6%), with an observed absolute decrease in clinically significant bleeding of 5%. Accounting for an estimated rate of persistently occlusive thrombosis of 15% at 6 weeks (randomization exclusion), and an anticipated non-retention rate of 25% for the primary endpoint at 1 year follow-up, a **total randomized population of 420 participants is targeted to meet study goals of a total of 316 participants in the primary analysis population (1 year follow-up primary endpoint).** Based on most recent randomization rates (28 June 2019) we estimate a total enrollment of 609 in the randomized and observational components of the Kids-DOTT study. The bivariate endpoint analysis statistical function for the completed trial is graphically depicted in **Figure 2**. The methods used to define the bivariate decision curve are described in the SAP. The SAP also describes how the decision curve changes when the event rate differs from the pre-trial design.

As reflected in the Statistical Analysis Plan, the risk differences (absolute risk reduction, ARR) for both the primary efficacy and primary safety endpoints will be used with the curve in **Figure 2** to determine the non-inferior decision. The decision curve in **Figure 2** (red line) is based on the original design assumption of a 10% risk for recurrent VTE and a 10% risk for clinically significant bleeding. Based on these assumptions, 570 randomized patients would be expected to produce 57 primary efficacy events and 57 primary safety events in the RCT primary analysis population. With the current risk of recurrent VTE (3%) and bleeding (1%) the decision curve is shifted toward the non-inferiority bound (**Figure 2** blue line). **Figure 2** shows the decision curve with the anticipated 316 subjects in the randomized treatment study (dashed green line). The methods for deriving these decision curves are provided in the SAP.

Figure 2: Bivariate decision criteria.



I. Data Management and Security

During the pre-NIH and NIH award period, data management and security were facilitated by CPC Research via a vendor-hosted, web-based, secure, user-restricted, password-protected, Electronic Data Capture (EDC) system, DATATRAK™. Data export and transfers to the University of Colorado-based lead biostatistician at the DCC are executed via a secure, user-restricted, password-protected server that resides behind the firewall at the University of Colorado School of Public Health. Database lock of this 'primary database' occurred in March 2021. A 'secondary' REDCap database hosted at JHACH will allow collection of continued 2-year follow-up visits and outcome events. Completion of all study visits is anticipated to occur by January 2022.

At the participating site level, the EDC system is used by Principal Investigators (PIs) and their designees for participant enrollment, and data collection, and query resolution. Data collection in the EDC system includes protected health information (PHI), limited to date of birth, and dates of events. In addition to using the EDC system, PIs at participating sites will maintain a local "Kids-DOTT participant key" as a password-protected file on a secure shared drive behind the institutional firewall. This key will consist of each participant's unique study ID code (centrally generated, via the EDC system) along with his/her Medical Record Number at the local medical institution. Any hard copy records containing PHI – including the regulatory binder for the trial as well as individual participant study binders -- will be kept in a locked file cabinet under the local PI's direct oversight.

At the CCC level, administrative access to the Kids-DOTT instance in the EDC system is granted to the CCC project managers on a limited basis. Specifically, this user-restricted role is used for query generation, and has "view-only" access.

In addition, the Johns Hopkins All Children's Pediatric Biorepository at the CCC, serving as the central biorepository for the trial, facilitates data management and security by means of a part-11-adherent web-based LIMs system (STARLIMS™, Abbot Informatics), that affords password-protected, user-restricted access to Biorepository staff only, and consists of PHI-free data on specimen/derivative inventory and pre-analytical quality assurance.

J. Data and Safety Monitoring Plan

As of January 2021, all data for the primary safety and efficacy endpoints have been collected and reviewed by the NHLBI DSMB. Therefore, the DSMB has concluded their meetings and there will be no further data safety monitoring reviews.

1. AE/SAE Reporting Plan

AEs and SAEs were collected from time of randomization to the end of the 12 week study window (12 weeks plus 10 days post-diagnosis). AEs were not collected on those patients who are assigned to a parallel cohort group or withdrawn withdrawn prior to randomization. At the time of this protocol amendment, all participants are past the AE collection window and no further AE reporting is required.

Outcome events - Recurrent VTE, Bleeding Events, and Death:

Recurrent VTE, bleeding events (major and clinically-relevant non-major), PTS, and death will be considered outcome events rather than adverse events.

Adjudication of outcome events:

Outcome events will be centrally adjudicated via an independent, blinded Clinical Endpoint Adjudication Committee (CEAC). Please see the Manual of Operations (MOO) for submission instructions.

2. Deviation Reporting Guidelines

A protocol deviation is defined as a variation from the protocol-directed conduct of a clinical trial. Any non-compliance with the study protocol, GCP, ICH guidelines, or a protocol-specific requirement is considered a protocol deviation. Protocol deviations will be entered into the EDC and reported to the site IRB per site policy.

Major Protocol Deviations

Major Protocol Deviations are defined as deviations that impact patient safety or the final outcome measures of the trial. Deviations that meet the defined criteria as Major Protocol Deviations will be reported within 5 days of identification of deviation to the CCC Project Manager and the site institutional review board (IRB) per local IRB policy.

Major Protocol Deviations include, but are not limited to:

1. Inappropriate enrollment; expired protocol*, violation of eligibility criteria or incomplete consent documentation*
2. Violation of any site specific IRB requirements (e.g. If sites IRB requires both parents to sign consent)
3. Randomization of patient outside randomization visit window (week 6) or other inappropriate randomization
4. Failure to report SAE in the 24 hour time period following knowledge of SAE*
5. Failure to provide source documentation of a primary efficacy or safety outcome, as well as death event, for central adjudication by the Clinical Endpoint Adjudication Committee (CEAC).

*items are identified as major protocol deviations, but do not disqualify participant's data to be included in the per protocol analysis.

Minor Protocol Deviations

Minor Protocol Deviations are defined as deviations that do not impact patient safety or the final outcome measure of the trial, but do not follow study specified guidelines. All deviations that are not determined to be major deviations are to be recorded as minor deviations.

Minor Protocol Deviations include, but are not limited to:

1. Missed visits or visits outside study windows (except missed/out-of-window for week 6 visit, which constitutes a MAJOR Deviation)
2. Missed laboratory samples that are not related to patient eligibility or study outcome (includes research specimens)
3. Lack of participant documentation (e.g., participant diary/calendar) of study medication administration and untoward events
4. Missed PTS evaluation (unless visit completed via phone)

5. Unanticipated Problem Reporting Guidelines

Unanticipated problems encountered or uncovered by a participating PI must be promptly reported to Dr. Neil Goldenberg and the site's Project Manager via email. Unanticipated problems must also be reported to the local IRB or EC as per local IRB/EC policies.

K. Data Sharing

In accordance with the NIH U-award (Cooperative Agreement) funding for this study and NIH data sharing policies, following completion of last-patient-last-visit on the study and database close and lock procedures (estimated: April 2022), a de-identified dataset exported from the study database will be transmitted by the Data Coordinating Center to the NHLBI Biologic Specimen and Data Repository (BioLINCC). This dataset will consist of individual subject-level data without identifiers, accompanied by unique subject ID.

L. Biospecimen Sharing

In accordance with the NIH U-award (Cooperative Agreement) funding for this study and NIH biospecimen sharing policies, a representative sample of the trial-derived biospecimen bank (see also Aim #4, p. 4) will be shipped from the study's central biorepository (the Johns Hopkins All Children's Pediatric Biorepository; see p. 8) to the NHLBI BioLINCC. Specifically, biospecimens shared with the NHLBI BioLINCC will consist of proportion of banked aliquots of each specimen type, on a per-patient, per-visit basis. As is also reflected in the laboratory section of the Manual of Operations, these specimens are coded via a 2D barcode embedded in the aliquot tubes. A linker file between 2D barcode and unique subject ID will be transmitted by the JHAC Pediatric Biorepository to the NHLBI BioLINCC. All biospecimens will have been internally monitored against the associated signed informed consent documents prior to transfer of biospecimens to NHLBI BIOLINCC.

M. Human Subject Research Considerations

1. Risks to Study Participants

The shortened-duration anticoagulation (6 week arm) may incur an increased risk of recurrent VTE, but this risk is likely minimized by randomization to this arm only among patients who have no evidence of completely-occlusive thrombosis after 6 weeks of initial therapy. Furthermore, if an increased risk of recurrent VTE indeed exists in this carefully defined patient group, such risk may be offset by a decreased risk of bleeding potentially offered by abbreviated anticoagulation.

As discussed in the consent document, recurrent VTE can include thrombosis in the same vein, a different vein, or pulmonary embolism. In the latter case, recurrent VTE can be fatal. Whether the risk of recurrent VTE is increased among children given a shorter course of anticoagulation therapy has not been determined, and will be evaluated in this study. Risks of bleeding in patients treated with anticoagulation are reduced by anticoagulant monitoring; nevertheless, the risk of major bleeding in patients given a standard therapeutic course of anticoagulation is 2% (Monagle et al., 2008). Such major bleeding includes bleeding in the brain or retroperitoneum, bleeding associated with a significant decline in hemoglobin in a 24-hour period, and bleeding requiring surgical intervention to establish hemostasis. These types of major bleeding can be life threatening. There is no evidence for a detectable difference in risk of major bleeding between the use of unfractionated heparin or LMWH (particularly, enoxaparin) as initial (i.e., acute period) therapy, nor between the use of LMWH (particularly, enoxaparin) and warfarin as extended (i.e., subacute therapy) [Monagle et al., 2008]. Whether the risk of major bleeding is decreased among children given a shorter course of anticoagulation therapy has not been determined, and will be evaluated in this study. Minor bleeding episodes (those not described above, such as nosebleeds or bleeding from lacerations that do not require surgical intervention and do not result in a brisk drop in hemoglobin) are more frequently observed than major bleeding events. The rate of minor bleeding episodes has been difficult to quantify in pediatric and adult studies, but may be as high as 20% (Monagle et al., 2008). Previous published pediatric experience with therapeutic dalteparin for acute VTE demonstrated no major hemorrhagic events among 29 children. Minor bleeding episodes developed in 4% of 48 children receiving either VTE prophylaxis or acute VTE therapy. No additional adverse events were reported.

2. Alternative Treatments Considered

An alternative to this research is to not participate and have the length of treatment decided by the treating hematologist. However, if an increased risk of recurrent VTE or PTS among patients receiving shortened therapy is demonstrated by this study, a future study may then compare 3 months of therapy (on one arm) versus 6 weeks of standard-dose anticoagulant therapy immediately followed by 6 weeks of low-dose anticoagulant therapy (on a second arm) in the management of children with clot resolution at 6 weeks.

3. Adequacy of Protection Against Risks

With regard to risks of anticoagulation, participants in whom bleeding develops will be instructed to seek medical attention. However, it should be noted that this study involves either standard duration of anticoagulation or else shortened duration of anticoagulation, and is therefore not anticipated to engender greater bleeding risk than standard care. With regard to the risk of recurrent VTE, participants will be instructed to seek medical attention for difficulty breathing, chest pain, severe or persistent headache, and extremity pain or swelling. Furthermore, interim telephone assessments for these symptoms will be conducted (i.e., best efforts made to contact the participant/parents) at 2, 4, and 5 months, in addition to the scheduled follow-up visits at 6 months, 12 months, and 2 years. With regard to PTS risks, patients with completely-occlusive thrombus at 6 weeks will not be eligible for randomization to shortened-duration anticoagulation, With regard to participant confidentiality, participant identifiers will be highly limited (i.e., Health Insurance Portability and Accountability Act [HIPAA] "limited data set") in the database, and a unique study code will be used in lieu of patient names. These data will be kept for as long as necessary to conduct this and any future research and to comply with legal obligations related to research. A copy of all consent forms, which will contain participant names, will be retained in a secure and locked file in the office of the local site principal investigator. A key will be securely stored separately at the local institution from all study documents that will link the participant name to the study code. The study will be conducted under the Declaration of Helsinki and International Conference on Harmonization guidelines.

Non-English speaking families will be provided with an informed consent written in a language understandable to them and a translator. To the extent permissible by local IRB policy, a short form (in the patient's native language) may be used in lieu of a fully translated informed consent form.

4. Special Consent/Assent Plan

As this study specifically addresses the pediatric population, assent must be obtained per local IRB/EC policy.

5. Potential Benefits

No definite direct benefit to the participant is expected from this study. There is a possible direct benefit in the form of a decreased bleeding risk among patients treated with shortened duration anticoagulation; however, no such benefit may be shown by the study.

6. Incentives or Rewards Offered for Participation

Participants will be compensated for completion of the 1-year visit. In EU sites, participants will be reimbursed for travel expenses associated with completion of the 1-year visit.

L. Summary of Knowledge to be Gained:

The knowledge gained from this study may improve our understanding of the natural history of VTE response to anticoagulant therapy and whether this response impacts upon long-term patient outcomes, such as recurrent VTE and the development of PTS. Moreover, the knowledge gained from this research may provide the foundation for a more rational approach by which to tailor optimal duration of anticoagulation for venous thrombosis in children in the future. Finally, the findings of secondary analyses promise to provide important additional outcomes data in relation to anticoagulant drug types, to supplement that which has been published to date.

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Appendix 1. Participating (including active and planned) institutions

(May not be all inclusive list as it will be updated only at the time of other needed protocol modifications)

Site Name / University Affiliation (if applicable)	City	State or Province	Country	Principal Investigator
Akron Children's Hospital / Northeast Ohio Medical University	Akron	OH	U.S.A.	John Fargo, MD
Arkansas Children's Hospital	Little Rock	AR	U.S.A.	Shelley Crary, MD
Boston Children's Hospital / Harvard University	Boston	MA	U.S.A.	Rachael Grace, MD
Charite Hospital	Berlin	---	Germany	Susanne Holzhauer, MD
Children's Hospital at Oklahoma University Medical Center / Oklahoma University College of Medicine	Oklahoma City	OK	U.S.A.	Osman Khan, MD
Children's Hospital Pittsburgh / University of Pittsburgh	Pittsburgh	PA	U.S.A.	James Cooper, MD
Children's Medical Center of Dallas / University of Texas Southwestern	Dallas	TX	U.S.A.	Ayesha Zia, MD
Children's of Alabama / University of Alabama Birmingham	Birmingham	AL	U.S.A.	Lee Hilliard, MD
Children's Healthcare of Atlanta / Emory University	Atlanta	GA	U.S.A.	Gary Woods, MD
Children's Hospital at Montefiore / Albert Einstein College of Medicine	Bronx	NY	U.S.A.	Jennifer Davila, MD
Children's Hospital Oakland	Oakland	CA	U.S.A.	Titi Singer, MD
Children's Hospital of Los Angeles / University of Southern California	Los Angeles	CA	U.S.A.	Julie Jaffray, MD
Children's Hospital of the King's Daughters	Norfolk	VA	U.S.A.	Eric Lowe, MD
Children's Hospital Orange County / University of California - Irvine	Irvine	CA	U.S.A.	Arash Mahajarin, MD
Children's Mercy Hospital / University of Missouri-Kansas City	Kansas City	MO	U.S.A.	Shannon Carpenter, MD
Cincinnati Children's Hospital / University of Cincinnati	Cincinnati	OH	U.S.A.	Cristina Tarango, MD
Cohen Children's Medical Center / Hofstra University-Northshore Long Island Jewish	New Hyde Park	NY	U.S.A.	Suchitra Acharya, MD
Dell Children's Medical Center of Central Texas	Austin	TX	U.S.A.	Robert Mignacca, MD
Detroit Children's Hospital / Wayne State University	Detroit	MI	U.S.A.	Madhvi Rajpurkar, MD

Site Name / University Affiliation (if applicable)	City	State or Province	Country	Principal Investigator
Doernbecher Children's Hospital / Oregon Health Sciences University	Portland	OR	U.S.A.	Kristina Haley, DO
Emma Children's Hospital / University of Amsterdam	Amsterdam	---	Netherlands	Marjolein Peters, MD
Kalispell Regional Medical Center	Kalispell	MT	U.S.A.	Courtney Lyle, MD
Hamilton Health Sciences Corporation / McMaster University	Hamilton	Ontario	Canada	Anthony Chan, MD
Helen Devos Children's Hospital / Michigan State University	Grand Rapids	MI	U.S.A.	Deanna Mitchell, MD
Hershey Medical Center / Penn State	Hershey	PA	U.S.A.	Smita Dandekar, MD
Hospital for Sick Children / University of Toronto	Toronto	Ontario	Canada	Leonardo Brandao, MD
Indiana Hemophilia and Thrombosis Center	Indianapolis	IN	U.S.A.	Charles Nakar, MD
Johns Hopkins All Children's Hospital / Johns Hopkins University	St. Petersburg	FL	U.S.A.	Marisol Betensky, MD
Johns Hopkins Children's Center / Johns Hopkins University	Baltimore	MD	U.S.A	Courtney Lawrence, MD
Norton Children's Hospital / University of Louisville	Louisville	KY	U.S.A.	Kerry McGowan, MD
Lucile Packard Children's Hospital / Stanford University	San Francisco	CA	U.S.A.	Clara Lo, MD
Lurie Children's Hospital / Northwestern University Feinberg School of Medicine	Chicago	IL	U.S.A.	Rukhmi Bhat, MD
Medical University of South Carolina / University of South Carolina	Charleston	SC	U.S.A.	Shayla Bergmann, MD
Medizinishe Universitat Wien / Medical University of Vienna	Vienna	---	Austria	Christoph Male, MD
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Appendix 2: Kids-DOTT Secondary Manuscripts Approved to date by the Publications Committee and Steering Committee

1. Complete veno-occlusion following an initial six weeks of anticoagulant therapy for first-episode provoked VTE and the risk of adverse outcomes (srVTE, PTS) in patients < 21 y.o.
   (DCC: CPC Clinical Research)
2. Durability of Kids-DOTT RCT Primary Findings at 2 Year Follow-up
   (DCCs: CPC Clinical Research and Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
3. Prevalence of Persistent APA and APS and associations with outcomes in patients <21 y.o. with first-episode acute provoked VTE
   (DCCs: CPC Clinical Research and Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
4. Predictors of clinically-significant PTS in patients <21 y.o. with first-episode provoked VTE
   (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
5. Predictors of symptomatic recurrent VTE in patients <21 y.o. with first-episode provoked VTE
   (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
6. Predictors of clinically-relevant bleeding in patients <21 y.o. with first-episode provoked VTE
   (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
7. Clinical characteristics, anticoagulant therapy, outcomes, and prognostic factors in patients <21 y.o. with first-episode provoked CSVT
   (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
8. Clinical characteristics, anticoagulant therapy, outcomes, and prognostic factors in patients <21 y.o. with first-episode provoked splanchnic venous thrombosis
   (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
9. Clinical characteristics, anticoagulant therapy, outcomes, and prognostic factors in cancer patients <21 y.o. with first-episode provoked VTE during remission
   (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
10. Clinical characteristics, anticoagulant therapy, outcomes, and prognostic factors in patients <21 y.o. with first-episode provoked non-proximal PE with underlying DVT
    (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
11. Clinical characteristics, anticoagulant therapy, outcomes, and prognostic factors in patients <21 y.o. with first-episode provoked right atrial thrombosis
    (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
12. Clinical characteristics, anticoagulant therapy, outcomes, and prognostic factors in patients <21 y.o. with first-episode central venous catheter (CVC)-related DVT
    (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)
13. Anticoagulant medication adherence in the treatment of provoked VTE in patients <21 y.o.: Characterization, associated factors, and VTE outcomes
    (DCC: Johns Hopkins All Children's DCC for Pediatric Multicenter Studies)

Prospective Multi-Center Evaluation of the Duration of Therapy for Thrombosis in Children
(the "Kids-DOTT" Trial)

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