

COVID-19 Anticoagulation in Children - Thromboprophylaxis (COVAC-TP) Trial

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I. HYPOTHESES AND SPECIFIC AIMS/PURPOSE

A. Statement of Purpose

The purpose of this study is to evaluate the safety, dose-requirements, and exploratory efficacy of twice-daily subcutaneous enoxaparin as in-hospital venous thromboembolism (VTE) prophylaxis in children (birth to 18 years) hospitalized with signs and/or symptoms of SARS-CoV-2 infection (i.e., COVID-19) including COVID-19 multisystem inflammatory syndrome (CMIS)

B. Principal Aims and Hypotheses

Specific Aim 1: To investigate the safety of in-hospital thromboprophylaxis with twice-daily low-dose enoxaparin thromboprophylaxis (starting dose, 0.5 mg/kg subcutaneously q12 hours, adjusted to achieve a 4 hour post-dose anti-factor Xa level of 0.20-0.49 anti-Xa U/mL) in children hospitalized with COVID-19 related-illnesses, as measured by the cumulative incidence of ISTH-defined [10] clinically-relevant bleeding (primary endpoint).

Hypothesis 1: The observed cumulative incidence of ISTH-defined clinically-relevant bleeding is $\leq 2.6\%$ (upper limit of 90% confidence interval: $\leq 11.8\%$) among children with COVID-19 who receive in-hospital thromboprophylaxis with twice-daily low-dose enoxaparin.

Specific Aim 2: To determine the median twice-daily enoxaparin dose, as measured in mg/kg, required to achieve a 4 hour post-dose anti-factor Xa level of 0.20-0.49 anti-Xa U/mL in children hospitalized with COVID-19 related-illnesses, and to compare dose-requirements by age group (birth to <1 year old, 1-<6 years old, 6-<13 years old, and 13-<18 years old).

Hypothesis 2: Median dose-requirement for anti-Xa-targeted thromboprophylaxis with twice-daily enoxaparin, as measured in mg/kg, in children hospitalized with COVID-19 are associated with age, with younger age groups requiring higher doses.

Specific Aim 3 (Exploratory): To investigate, on an exploratory basis, the efficacy of in-hospital thromboprophylaxis with twice-daily enoxaparin in children hospitalized with COVID-19, as measured by the proportion of serial D-dimer levels obtained at standardized time points that are < 2 times the upper limit of normal ($< 2 \times \text{ULN}$) values for age (Aim 3a; surrogate marker of efficacy), the cumulative incidence of radiologically-confirmed HA-VTE (Aim 3b; clinical efficacy), and the median duration of in-hospital increased respiratory support (new requirement for high-flow nasal cannula, non-invasive ventilation, and/or mechanical ventilation, relative to any at-home baseline requirement; Aims 3c, clinical efficacy).

II. BACKGROUND AND SIGNIFICANCE

VTE is a serious condition in children associated with significant morbidity. Adverse VTE outcomes include VTE-related mortality, recurrent VTE, and development of chronic venous insufficiency following deep venous thrombosis (post-thrombotic syndrome). Given these adverse outcomes, as well as recent recognition of VTE as the second leading cause of preventable harm in hospitalized children (after central line associated blood stream infections; CLABSI) [1], a national patient safety initiative in the U.S., supported by the Children's Hospitals Association Solutions for Patient Safety network, has been undertaken to reduce the incidence of hospital-associated VTE (HA-VTE) in children. While pharmacological thromboprophylaxis with various anticoagulants (including low molecular weight heparins and the direct oral anticoagulants) has been shown to be safe and effective in hospitalized adults, both safety and efficacy among hospitalized children have yet to be fully established.

In order to optimize benefit-risk ratio for target populations in future trials of anticoagulant thromboprophylaxis in hospitalized children, the PI and colleagues have developed risk models for HA-VTE in several important hospitalized pediatric populations, including non-critically ill children, critically-ill children without underlying cardiac disease, and critically-ill children following cardiac surgery or cardiac catheter-based therapeutic intervention [2–5]. These models share common features of central venous catheterization, severe infection or systemic inflammatory state, and anticipated length of stay (LOS) >3 days as statistically-significant, independent risk factors for HA-VTE in hospitalized children. In the absence of efficacy and safety data from pediatric trials, clinicians across the U.S., Canada, Europe and many other countries/regions have, in recent years, used low-dose low molecular weight heparins (LMWH; most often, enoxaparin) as primary thromboprophylaxis in hospitalized children who exhibit these and/or other high-risk features for the development of in-hospital VTE.

A novel coronavirus, SARS-CoV-2, is responsible for a rapidly spreading pandemic that has reached 160 countries, causing infection in over 500,000 individuals, and 25,000 deaths, as of April 1, 2020. The SARS-CoV-2 illness, known as COVID-19, exhibits a range of disease severity, from asymptomatic infection to respiratory failure, multi-organ failure, and death. Among hospitalized patients, COVID-19 is characterized by atypical pulmonary infiltrates and a severe inflammatory response with which marked coagulation activation, as evidenced by marked elevation in plasma D-dimer levels. A recent retrospective analysis from China demonstrated reduced mortality and reduced LOS among hospitalized patients (primarily adults) with COVID-19 and markedly-elevated D-dimers who received anticoagulation (predominantly, LMWH) [6]. Accordingly, the International Society on Thrombosis and Haemostasis (ISTH) has recently recommended prophylactic anticoagulation be strongly considered in patients hospitalized for COVID-19 [7]. Similarly, the American Society of Hematology has recommended that “all patients hospitalized with COVID-19 should receive pharmacologic thromboprophylaxis” and recommend participation in “well-designed clinical trials and/or epidemiologic studies when they become available.” [8] Children with COVID-19 have also presented with

CMIS, a Kawasaki-disease-like illness, presenting with severe systemic inflammatory disease affecting multiple systems beyond the respiratory system. [9]

Hospitalization of children infected with SARS-CoV-2 have increased across many children's hospitals in the U.S. with nearly 1% of the infected pediatric population anticipated to develop acute respiratory distress syndrome [10]. Many children hospitalized with COVID-19 are exhibiting markedly elevated D-dimer levels [11] much as has been observed in hospitalized adults, and it is expected that these children will similarly exhibit a heightened VTE risk. Based on this urgent and time-sensitive clinical need, and given that anticoagulant prophylaxis against HA-VTE in children is used selectively in routine care at children's hospitals across the U.S. but is not yet supported by safety data from multicenter clinical trials, the objective of this proposal is to rapidly conduct a phase 2 multicenter trial of low-dose enoxaparin thromboprophylaxis in children newly-hospitalized with COVID-19. The study proposed herein will leverage an existing network and clinical coordinating center (CCC) infrastructure of the NIH NHLBI U01 Prospective Multi-Center Evaluation of the Duration of Therapy for Thrombosis in Children (Kids-DOTT).

This proposal is significant in that it addresses a critical need for establishing safety of prophylactic anticoagulation in hospitalized children who are at heightened risk for HA-VTE. Furthermore, this proposal is innovative, in that it seeks to establish first multicenter evidence on safety of prophylactic anticoagulation for the prevention of HA-VTE in children, with a focus on the especially-heightened VTE risk population of pediatric patients hospitalized with COVID-19 related-illnesses. The work under this supplement is a logical extension of the parent award, and will provide complementary knowledge to the findings derived from the Kids-DOTT trial, addressing a critical gap in knowledge in the pediatric VTE field. The proposed trial addresses the same problem as the parent award (i.e., VTE in children) and employs the same therapeutic agents (i.e., conventional anticoagulants, which have consisted of the LMWH enoxaparin in >95% of patients).

III. PRELIMINARY STUDIES/PROGRESS REPORT:

Based on a PubMed search on 13April2020, no prior studies of safety, dose-requirement, and/or efficacy of twice-daily enoxaparin thromboprophylaxis in hospitalized children, with or without COVID-19, have been published. Based on clinicaltrials.gov and eudract.ema.europa.eu search on 13April2020, no such studies have been registered on clinicaltrials.gov or with EudraCT in Europe.

IV. RESEARCH METHODS: SUMMARY OF STUDY RATIONALE

A. Primary Outcome

PRIMARY SAFETY: Occurrence of clinically-relevant (i.e., major plus clinically relevant non-major [CRNM]) bleeding within 30 days.

Based upon International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee standardized definitions for pediatric trials [12], “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)

DOSE REQUIREMENT: Median twice-daily enoxaparin dose, as measured in mg/kg, required to achieve a 4 hour post-dose anti-factor Xa level of 0.20-0.49 anti-Xa U/mL.

EXPLORATORY EFFICACY: Proportion of plasma D-dimer levels <2x ULN; cumulative incidence of VTE; and duration of assisted ventilation.

C. Endpoint Adjudication

The primary safety outcome (clinically-relevant bleeding) and exploratory clinical efficacy outcome of recurrent VTE, as well as all death events, will be centrally adjudicated via an independent Clinical Endpoint Adjudication Committee (CEAC), using a standardized process delineated in the CEAC charter. Upon reporting of these outcome events, de-identified information on pertinent history, physical exam findings, imaging studies, laboratory studies, and other pertinent information from the medical record corresponding to these outcome events (clinically-relevant bleeds) will be submitted by the study team at participating sites for review by the clinical experts on the committee.

D. Summary of Research Methods and Study Design

The study design is a phase 2, single-arm, open-label, non-randomized clinical trial conducted among the Kids-DOTT Investigators Group, at 12-15 of the Kids-DOTT participating centers. The list of participating Kids-DOTT centers (including primary and alternate/supplemental sites) is shown in Appendix 1. Study activity at each site will be

overseen by either a pediatric hematologist, pediatric intensivist, or pediatric hospitalist as the site principal investigator, in close collaboration with sub-investigators from the other two aforementioned specialties.

The Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC) for this non-blinded, non-randomized phase 2 trial are at Johns Hopkins All Children's Hospital (JHACH; St. Petersburg, FL), led by Johns Hopkins University School of Medicine faculty based on that campus (Appendix 2. CCC). Coordinating center personnel have extensive experience in the conduct of numerous large collaborative clinical trials, with specific expertise in pediatric phase 1-3 trials. CCC and DCC key personnel include:

Overall (National) Principal Investigator:	Anthony Sochet, MD, MSc
Steering Committee Chair:	Neil Goldenberg, MD, PhD
Clinical Endpoint Adjudication Ctte Chair:	Robert Sidonio, MD
Data and Safety Monitoring Board Chair:	Sarah O'Brien, MD, MPH
Medical Safety Officer:	Neil Goldenberg, MD, PhD
Multi-Site Project Managers:	Fatima Tariq, MS (CCC) Nuredin Joechar, MBA-IT (DCC)
Lead Biostatistician:	Ernest Amankwah, PhD
Biorepository Manager:	Billy Schleif, MS, MT

Anticoagulant (low-dose enoxaparin) thromboprophylaxis dosing regimen is as follows for inpatient use only:

- Enoxaparin starting dose 0.5 mg/kg (max starting dose: 60 mg) subcutaneously q12 hours, adjusted to achieve a 4 hour post-dose anti-factor Xa level of 0.20-0.49 anti-Xa U/mL after the 1st or 2nd dose.
 - For anti-Xa values <0.20 U/mL, the enoxaparin dose will be increased by 10-20%, and a 4 hour post-dose anti-Xa level will be obtained after the 1st or 2nd dose at the new dosing regimen.
 - For anti-Xa values ≥0.5 U/mL, the enoxaparin dose will be decreased by 10-20%, and a 4 hour post-dose anti-Xa level will be obtained after the 1st or 2nd dose at the new dosing regimen.

The Schedule of Assessments is shown in Table 1. SAE monitoring and safety laboratory monitoring occurs on days 1-3, and on days 7 and 14 if the patient is still hospitalized. For all participants, pertinent clinical data will be captured as follows: results of coagulation and thrombophilia testing; nature of any major or clinically-relevant non-major 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 other intervention required—see also Data and Safety Monitoring Plan section); and nature of any new onset VTE (with detail as to signs/symptoms and anatomic site). PDFs of the REDCap electronic case report forms (eCRFs), as well as SAE report forms, are provided in the Manual of Operations. All SAEs and enoxaparin regimen adherence will be tracked

throughout hospitalization, and SAEs will continue to be tracked through 30 days post-enrollment.

Children will complete their participation in the trial at the 30 days (+/- 2 days) post-enrollment end-of-study telephone visit. As noted previously, the primary safety endpoint collection also occurs at the 30 days (+/- 2 days).

E. Description of Population to be Enrolled

1. Target Enrollment

The target accrual is based on the primary endpoint (safety). The safety population is defined as all patients who received at least one dose of the enoxaparin regimen. In order to achieve adequate power and precision for determination of safety in the primary analysis (see also section G, below), the target enrollment is 38 evaluable children, from among a total of 12-15 participating sites. Participants who do not received at least one dose of the enoxaparin regimen (i.e. early termination, withdrawal of consent) will be replaced. Anticipating an 85% retention rate, we will enroll up to 45 participants. Both males and females of all races and ethnic groups are eligible for this study.

Table 1. Schedule of Assessments.

Assessment	Screening (Within 72 hours of hospital admission)	Enrollm ent Day 0	Day 1	Day 2	Day 3 *	Day 7 *	Day 14 *	Day 30 (+/- 2 days)
Informed consent		X						
Enrollment		X						
Full H&P	X							
Focused H&P			X	X	X	X	X	
Weight	X							
CBC with platelet count	X				X	X	X	
PT and aPTT ¹	X				X	X	X	
Fibrinogen ¹	X				X	X	X	
Serum creatinine	X				X	X	X	
Urine pregnancy screen ¹	X							
Research blood specimen ²		X	X	X	X	X	X	
Anti-factor Xa level ^{1,3}			X	+/- X				
SAE Monitoring			X	X	X	X	X	X
Bleeding event (based on focused interim H&P)			X	X	X	X	X	X
VTE event (based on focused interim H&P, with radiological confirmation when suspected clinically)			X	X	X	X	X	X
Telephone visit ⁴								X

¹ Obtained for research purposes if not already being obtained clinically.

² For participants <20kg: (1) 3mL blue top tube and (1) 4mL CPT Tube (7mL total). For participants ≥20kg, (1) 3mL blue top tube and (2) 4mL CPT tubes (11mL total). Research blood collection is for central research lab testing of D-dimer, Clot Formation and Lysis (CloFAL) assay, IL-6, and anti-SARS-CoV-2 IgG, as well as banking plasma, DNA isolated from the buffy coat, and peripheral blood mononuclear cells (PBMCs) for future research.

³ Obtained at 4 hours after 1st or 2nd dose of enoxaparin, at initial dosage (mg/kg) and any subsequent change in dosage.

⁴ Focused, scripted assessment of symptoms of potential concern for bleeding events, VTE events, and SAEs. Refer to Manual of Operations.

* If still hospitalized.

Abbreviations: H&P, history and physical exam; CBC, complete blood count; PT, prothrombin time; aPTT, partial thromboplastin time; SAE, serious adverse events; VTE, venous thromboembolism; CT, computed tomography.

2. Inclusion Criteria

Inclusion Criteria for COVID-19 Infected Patients:

1. Children (birth to <18 years of age)
2. Positive nucleic acid test, antigen testing, or antibody testing for SARS-CoV-2 within the past 7 days
3. Hospitalized <72 hours post-admission
4. One or more signs and/or symptoms of COVID-19 illness within the past 72 hours, as follows:
 - i.) Cough
 - ii.) Fever (oral temperature >100.4°F/38°C)
 - iii.) Chest pain
 - iv.) Shortness of breath
 - v.) Myalgia
 - vi.) Acute unexplained loss of smell or taste
 - vii.) New/increased supplemental oxygen requirement
 - viii.) Acute respiratory failure requiring non-invasive or invasive ventilation
 - ix.) Encephalitis
5. Clinical suspicion that the above symptoms are related to COVID-19 infection and not an alternative etiology.

Inclusion Criteria for CMIS Patients Who Do Not Already Meet the Above Criteria for COVID-Infected Patients:

1. Children (birth to <18 years of age)
2. Signs and symptoms of COVID-19 Multi-System Inflammatory Syndrome (CMIS) including:
 - i.) fever \geq 3 days;
 - ii.) Two or more of the following:
 - a) Rash of bilateral non-purulent conjunctivitis or muco-cutaneous inflammation (oral, hands, or feet),
 - b) Hypotension or shock,
 - c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP),
 - d) Evidence of coagulopathy (by PT, PTT, or d-Dimer)
 - e) Acute gastrointestinal problems (diarrhea, vomiting, abdominal pain)
 - iii.) Elevated markers of inflammation (erythrocyte sedimentation rate, C-reactive protein, or pro-calcitonin);
 - iv.) No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndrome;
 - v.) Known exposure to a SARS-CoV-2 positive case, as documented by clinical history

3. Exclusion Criteria (for both COVID-19 and CMIS)

- 1) Patient's expected length of hospitalization is < 2 days
- 2) Receiving therapeutic dosing of anticoagulation (NOTE: pre-enrollment prophylactic enoxaparin administration is not an exclusion criterion)
- 3) Receiving ASA dosing > 5 mg/kg/day
- 4) Clinical-relevant bleeding (see criteria under Primary Outcome, below) within the past 72 hours
- 5) Platelet count <50,000/ μ L within the past 24 hours
- 6) Prothrombin time (PT) \geq 2 seconds above the upper limit of age-appropriate local reference range within 24 hours prior to enrollment, unless PT was <2 seconds above upper limit within 24 hours prior to start of anticoagulation for routine clinical care OR unless a PT mixing study at either of these time points indicates the absence of a coagulation factor deficiency*
- 7) Activated partial thromboplastin time (aPTT) \geq 4 seconds above the upper limit of age-appropriate local reference range within 24 hours prior to enrollment, unless PTT was <4 seconds above upper limit within 24 hours prior to start of anticoagulation for routine clinical care OR unless a PTT mixing study at either of these time points indicates the absence of a coagulation factor deficiency*
- 8) Fibrinogen level <75 mg/dL
- 9) Severe renal impairment, as defined by estimated glomerular filtration rate (eGFR) <31 mL/min/1.73 m², as calculated by the Schwartz formula
- 10) Parent or legally authorized representative unwilling to provide informed consent for patient participation.

*NOTE: A PT-based or PTT-based mixing study indicates the absence of a coagulation factor deficiency if the originally-prolonged clotting time in the assay does not correct to within the age-appropriate local reference range upon the addition of pooled normal plasma to patient plasma in a 1:1 ratio.

NOTE regarding pregnancy and eligibility:

A patient that is pregnant while enrolled in this study will remain eligible for this study.

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

There will be minimal laboratory assays, examinations, or other procedures performed solely for the purposes of this study and not currently part of best/standard clinical care.

The first is an additional 11 mL blood specimen (7mL in participants <20kg) obtained at visits on post-enrollment days 1 and 2 (and days 3, 7, and 14 if still hospitalized) for protocol-specified research laboratory investigations (D-dimer, IL-6, anti-SARS-CoV-2 IgG/IgM, and CloFAL assay) and future unspecified research (i.e., banking of plasma, DNA isolated from the buffy coat, and isolated PBMCs). 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 and COVID-19-related illness. The genetic investigations will involve candidate genes, a genome-wide association study (GWAS), and whole genome sequencing approaches in deoxyribonucleic acid. 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 COVAC-TP 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. The second procedure will be obtaining a contrast enhanced computed tomography scan of the chest within 24 hours preceding discharge from the hospital (if not already obtained clinically during hospitalization) to assess for pulmonary emboli. Throughout their study participation, up to and including visit 6, patients will be assessed for bleeding and VTE events by their inpatient medical provider team with any SAEs being documented in the case report forms (supported by source documentation in the patient's electronic medical record) and reported to the Medical Safety Officer (MSO) as described in Section J.2. The MSO will perform an independent determination of each SAE that has been locally determined by the responsible site PI, regarding relatedness to study intervention. If EITHER determination is that the SAE is "related", the SAE will be reported to the DSMB chair. The DSMB will then assess whether any action is needed, depending on the nature of the SAE. Adverse events (and symptoms of concern for possible VTE or clinically-relevant bleeding) will be further assessed at a long-term follow up visit 30 days (+/- days) after enrollment via telephone call from a study team member.

Screening/Within 72 hours of hospital admission (Day 0)

- Informed consent
- Enrollment
- Full medical history and physical exam
- Weight
- Initial plasma laboratory evaluation including the following (obtained as research purposes if not already obtained clinically)
 - Complete blood cell count with platelet count
 - PT and aPTT
 - Fibrinogen
 - Serum creatinine
 - Urine pregnancy screening (beta-HCG)
- Research blood specimen collection

Day 1 after enrollment (as inpatient)

- Interval focused interim history and physical with assessment for serious adverse events, bleeding event, and/or VTE event by inpatient medical provider
- Anti-factor Xa level
- Research blood specimen

Day 2 after enrollment (as inpatient)

- Interval focused interim history and physical with assessment for serious adverse events, bleeding event, and/or VTE event by inpatient medical provider
- Anti-factor Xa level (if enoxaparin dose sub- or supratherapeutic)
- Research blood specimen

Day 3 after enrollment (if still hospitalized)

- Interval focused interim history and physical with assessment for serious adverse events, bleeding event, and/or VTE event by inpatient medical provider
- Repeat plasma laboratory evaluation including the following (obtained as research purposes if not already obtained clinically)
 - Complete blood cell count with platelet count
 - PT and aPTT
 - Fibrinogen
 - Serum creatinine
- Research blood specimen

Day 7 after enrollment (if still hospitalized)

- Interval focused interim history and physical with assessment for serious adverse events, bleeding event, and/or VTE event by inpatient medical provider
- Repeat plasma laboratory evaluation including the following (obtained as research purposes if not already obtained clinically)
 - Complete blood cell count with platelet count
 - PT and aPTT
 - Fibrinogen
 - Serum creatinine
- Research blood specimen

Day 14 after enrollment (if still hospitalized)

- Interval focused interim history and physical with assessment for serious adverse events, bleeding event, and/or VTE event by inpatient medical provider
- Repeat plasma laboratory evaluation including the following (obtained as research purposes if not already obtained clinically)
 - Complete blood cell count with platelet count
 - PT and aPTT
 - Fibrinogen
 - Serum creatinine
- Research blood specimen

30 days (+/- 2 days) after enrollment

Patient will be assessed for SAEs, bleeding events, and VTE events via telephone call with a study team member using a standardized screening script.

Off-Study Criteria:

1. In the investigator's opinion, it is in the participant's best interest to discontinue participation.
2. Study discontinuation by sponsor, IRB, or other regulatory body.
3. 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 30-day visit window. Sites must document all attempts to contact the participant.

G. Potential Scientific Problems:

Although this study involves relatively minimal intervention relative to standard care for hospitalized children with potentially severe respiratory viral infections, the main potential problems and challenges involve maintaining adequate personal protection from the exposure and transmission of SARS-CoV-2 (the cause of COVID-19 disease). Accordingly, all interactions with participants will take place as part of each site's standard of care for patients with COVID-19. Clinical assessments and the procurement of biologic specimens will be obtained concurrent with routine clinical procedures so to limit the consumption of limited personal protective equipment. In order to reduce exposure of study personnel to patients positive for SARS-CoV-2 and reduce the consumption of PPE, informed consent will be obtained in accordance with FDA regulations (21 CFR 50.27(a)) that allow each site to obtain informed consent if the appropriate technology is available or utilizing the following steps:

- 1) An unsigned consent form will be provided to the parent/legal guardian by a health care worker that has already entered the patient's room
- 2) In the event direct communication with the parent/legal guardian and patient is not feasible or safe, the investigator (or designee) will arrange a three-way call or video conference with the parent/legal/guardian and impartial witness

- 3) Each site will utilize a standard practice to ensure all patients approached in a consistent fashion including:
 - a) Identification of who is on the call
 - b) Review of the informed consent with the parent/legal guardian and response to any questions they may have
 - c) Confirmation by the witness that the patient's questions have been answered
 - d) Confirmation by the investigator that the parent/legal guardian is consenting for the patient to participate in the study

If the informed consent document is obtained in person and cannot be removed from the patient's room and included in the study records due to infection control processes, the following measures will be considered compliant with FDA regulations for informed consent:

- 1) Attestations by the witness who participated in the call and by the investigator that the patient confirmed that they agreed to participate in the study and signed the informed consent; OR
- 2) A photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the patient.

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 the protocol-defined enoxaparin thromboprophylaxis regimen, as being consistent with their local standard practice. These potential challenges did not materialize as substantive issues in the Kids-DOTT phase 3 multicenter trial conducted by the same investigator group.

H. Data Analysis Plan:

The statistical analysis plan was developed by the lead trial biostatistician. Subject demographics and characteristics at study entry will be summarized with counts and percentages for categorical variables, and with means, standard deviations, medians, and interquartile ranges (IQR) as appropriate, for numeric variables. Missing data will not be imputed. Analysis of the primary endpoint will be conducted on the safety population, which includes all subjects who receive at least one dose of enoxaparin. The primary endpoint, cumulative incidence of ISTH-defined [11] clinically-relevant bleeding events during hospitalization, will be calculated with the corresponding exact (Clopper-Pearson) 90% confidence intervals (90% CIs). The precision of estimates for different cumulative incidences of clinically-relevant bleeds and corresponding 90% CIs are as follows: 0/38, 0% (0-7.6%); 1/38, 2.6% (0-11.8%); 2/38, 5.3% (0-15.7%). The secondary endpoint, twice-daily enoxaparin dose required to achieve target anti-Xa levels, will be summarized

with medians and IQRs for all the study participants combined and by age group. Medians will be compared across age groups, if there are adequate numbers in the groups, using the Kruskal-Wallis test and a *post-hoc* Bonferroni-adjusted Mann-Whitney U test, if needed. The tertiary endpoints (as outlined in Section IV.B) will be calculated as proportions and cumulative incidences with 90%CI, and medians with IQRs.

I. Data Management and Security

At the Data Coordinating Center (DCC) level, data management and security are facilitated via a JHACH-hosted, web-based, secure, user-restricted, password-protected, Electronic Data Capture (EDC) system, REDCap. When combined with the Standard Operating Procedures of the COVAC-TP trial DCC at JHACH (sponsoring institution), REDCap fosters 21CFR part 11 adherence. Electronic case report form (eCRF) additions, modification of programmed data quality assurance alerts, and programming of reports within the EDC system is overseen by the DCC. Data export and transfers to the JHACH-based lead biostatistician at the DCC are executed via a secure, user-restricted, password-protected server that resides behind the firewall at the Johns Hopkins University School of Medicine.

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 “COVAC-TP 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 COVAC-TP 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 within the eCRFs.

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 21 CFR part-11-adherent web-based LIMs system (STARLIMSTM, 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 Safety and Monitoring Plan

1. DSMP Summary

An independent Data and Safety Monitoring Board (DSMB) consisting of a pediatric hematologist, a pediatric critical care or hospital medicine physician, and a PhD-level

biostatistician will be established and supported via the Pediatric Data Coordinating Center at Johns Hopkins All Children's. The DSMB will convene at least quarterly throughout the trial, including interim analyses for safety monitoring, to review confidential and de-identified data. Criteria for halting enrollment pending further evaluation by the DSMB are shown in Table 2, below. At that time, the DSMB will consider a recommendation to terminate versus continue the trial, based on evaluation of most up-to-date literature on the rate of clinically-relevant bleeding among children hospitalized with COVID-19 outside of the trial.

A Medical Safety Officer (MSO) will function for additional safety oversight for the Overall PI, and to facilitate timely sponsor-level SAE review and communication with the DSMB. The MSO will perform an independent determination of each SAE that has been locally determined by the responsible site PI, regarding relatedness to study intervention. If EITHER determination is that the SAE is "related", the SAE will be reported to the DSMB chair. Reporting timelines are provided in the Manual of Operations

2. Protocol Stopping Criteria

Following its review of the DSMB Report and any other relevant data at each meeting, the COVAC-TP independent DSMB will make recommendations to the Steering Committee and the NHLBI Office of the Director regarding termination vs. continuation of the phase 2 clinical trial as noted in Table 2. These recommendations by the DSMB will consider the stopping rules and cumulative SAE profile to date and other relevant safety findings in the study, as well as trial quality and enrollment metrics. In the case of persistently poor trial enrollment metrics, the DSMB may recommend termination of the trial for futility, versus continuation of the trial with protocol modifications.

Reasons for early termination are as follow:

- Evidence of safety concerns—although stopping rules have been established as a guide, this can occur at any point during the study, based on the DSMB's review of cumulative data to date at scheduled or *ad hoc* DSMB meetings.
- Determination of futility: Evidence of persistently poor trial enrollment metrics, which cannot be (or has not been) remedied via protocol modification or other appropriate corrective action.

Table 2. Optimized Boundaries for Halting Enrollment (i.e., "Pause") Pending Further Evaluation by the DSMB.

# Patients who Received Enoxaparin Thromboprophylaxis	Pause if # of Patients with Clinically-Relevant Bleeding
<10	1
10-<20	2
20-<30	3
30-<38	4

3. SAE Reporting Plan

SAEs will be collected from time of enrollment to the end of the 30 day study window. Diseases or conditions that were present prior to the time of randomization should not be counted as adverse events unless they increase in grade or severity during the timeframe described above.

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious adverse event: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be reported within 24 hours of knowledge of the event. Please refer to the Manual of Operations for SAE reporting forms and guidelines.

Bleeding Events:

- Major bleeds and clinically-relevant non-major (CRNM) bleeds will be considered SAEs of particular interest (if they occur during the AE reporting window).
- Based upon ISTH standardized definitions for pediatric trials [10], "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, but not in an operating suite; 2) Bleeding for which medical attention is sought.

VTE events will be considered outcome events rather than SAEs, unless they otherwise fulfill the regulatory definition of an SAE (i.e., they will not fulfill the SAE criterion of investigator-defined “important medical events”).

Adjudication of clinically-relevant bleeding, VTE, and death:

The primary outcome on safety in regard to clinically-relevant bleeding, the tertiary outcome on clinical efficacy in regard to VTE events, and all death events will be centrally adjudicated via an independent, non-blinded Clinical Endpoint Adjudication Committee (CEAC) for this non-blinded, non-randomized phase 2 trial. Refer to the Manual of Operations for reporting forms and submission instructions.

4. 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 REDCap and reported to the site IRB per site policy. Deviations are reviewed in aggregate fashion at standing meetings of the COVAC-TP DSMB, via the DSMB report template. Any concerning trends can be further assessed via review of site-specific deviation logs by the COVAC-TP DSMB, as warranted, and upon request.

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. Failure to report SAE in the 24 hour time period following knowledge of SAE*
4. 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 Visits 4-6 if not hospitalized at time visit is scheduled)
2. Missed laboratory samples or radiographic imaging that are not related to patient eligibility or study outcome (includes research specimens)

5. Unanticipated Problem Reporting Guidelines

Unanticipated problems encountered or uncovered by a participating site PI must be promptly reported to the Overall PI and the CCC Project Manager via email. Unanticipated problems must also be reported to the IRB or as per IRB policy.

K. Human Subject Research Considerations

1. Risks to Study Participants

As discussed in the consent document, 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% [13]. Retrospective analysis of the Pediatric Health Information System (PHIS) revealed a combined minor and major bleeding rate of 5.6% in hospitalized children receiving thromboprophylaxis [14]. 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. 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 of VTE treatment (including standard-dose enoxaparin), but may be as high as 20% [13]. Minor bleeding episodes developed in 4% of 48 children receiving either VTE prophylaxis or acute VTE therapy. No additional adverse events were reported. Enoxaparin is used as first-line therapy for treatment dosing and prophylaxis for VTE in pregnant women because it does not cross the placenta into fetal circulation [15]. Therefore, exposure to enoxaparin does not pose risk to the developing fetus.

2. Alternative Treatments Considered

An alternative to this research is to not participate and have the prophylaxis approaches against HA-VTE determined by the primary medical team, with consultation of a pediatric hematologist as deemed clinically appropriate.

3. Adequacy of Protection Against Risks

With regard to risks of anticoagulation, participants in whom clinically-relevant bleeding develops in-patient (on enoxaparin prophylactic regimen) will receive appropriate medical attention, and those in whom bleeding develops as an outpatient (off enoxaparin prophylaxis) will be instructed to seek medical attention, as part of routine hospital discharge instructions, with re-enforcement by study personnel. However, it should be noted that this study involves standard prophylactic dosing of low-dose enoxaparin, and is therefore not anticipated to engender substantively greater bleeding risk than standard care, and is not expected to be associated with increased bleeding risk beyond 12 hours post-cessation of the in-patient low-dose enoxaparin regimen. 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 provided. 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 as per IRB policy. A subset of children will be unable to provide assent as a result of age, maturity, or severity of illness. These children qualify for a waiver of assent. The remainder of children will have assent without a signature obtained at the time of parental permission to both limit research staff exposure to COVID-19 to research staff.

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 risk for development of VTE; however, no such benefit may be shown by the study.

6. Incentives or Rewards Offered for Participation

There will be no compensation for participation in this study.

L. Summary of Knowledge to be Gained:

The knowledge gained from this study will advance our understanding of safety, dose-finding and (on an exploratory basis) efficacy of twice-daily low-dose enoxaparin thromboprophylaxis in children hospitalized with COVID-19, and more generally, hospitalized children who are at increased risk of VTE. The tertiary aim, investigating the effect of thromboprophylaxis on respiratory-related outcomes and D-dimer, will contribute to the currently limited understanding of the pathophysiology of COVID-19 disease in children.

V. REFERENCES

1. Goldenberg NA. Venous thromboembolism in children. Clin Adv Hematol Oncol. **2019**; 17(6):326–329.
2. Branchford BR, Mourani P, Bajaj L, Manco-Johnson M, Wang M, Goldenberg NA. Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. Haematologica. **2012**; 97(4):509–15.
3. Atchison CM, Arlikar S, Amankwah E, et al. Development of a new risk score for hospital-associated venous thromboembolism in noncritically ill children: findings from a large single-institutional case-control study. J Pediatr. **2014**; 165(4):793–8.
4. Arlikar SJ, Atchison CM, Amankwah EK, et al. Development of a new risk score for hospital-associated venous thromboembolism in critically-ill children not undergoing cardiothoracic surgery. Thromb Res. **2015**; 136(4):717–22.
5. Atchison CM, Amankwah E, Wilhelm J, et al. Risk factors for hospital-associated venous thromboembolism in critically ill children following cardiothoracic surgery or therapeutic cardiac catheterisation. Cardiol Young. **2018**; 28(2):234–242.
6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. **2020**; .
7. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. **2020**; .
8. American Society of Hematology. COVID-19 and VTE/Anticoagulation: Frequently asked questions. Accessed 04/18/2020 < <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>>
8. Kids-DOTT Investigators Group.
9. Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;DOI: [https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1).
10. Cruz AT, Zeichner SL. COVID-19 in Children: Initial Characterization of the Pediatric Disease. Pediatrics. **2020**; .
11. Wang Z, Zhu F, Wang C, et al. Children hospitalized with severe COVID-19 in Wuhan. Pediatr Infect Dis J. **2020**;39(7):e91-e94.
12. Mitchell LG, Goldenberg NA, Male C, et al. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. J Thromb Haemost. **2011**; 9(9):1856–8.
13. She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. J Med Virol. **2020**; .
14. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. **2020**; .
15. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. **2008**; 133(6 Suppl):887S-968S.
16. Amos LE, Silvey M, Hall M, Witmer CM, Carpenter SL. Primary thromboprophylaxis in hospitalized children: A multi-center retrospective analysis. Thromb Res. **2019**; 176:1–7

17. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. **2012**. 141(2 Suppl):e691S-e736S.

VI. APPENDICES

Appendix 1. Planned participating centers and site investigators.

Primary Centers

Site Name (Location)	Affiliation	PI /Sub-I(s)
All Children's Hospital Johns Hopkins Medicine (St. Petersburg, FL)	Johns Hopkins University	Sochet/Goldenberg/Morrison
Children's Hospital of Los Angeles (Los Angeles, CA)	Univ. of Southern California	Jaffray/Kamerkar/Cowell
Rady Children's Hospital (San Diego, CA)	University of California San Diego	Thornburg/Harvey/Fisher
Children's Medical Center of Dallas (Dallas, TX)	University of Texas Southwestern	Zia/McMichael/Linver
Cohen Children's Medical Center (New Hyde Park, NY)	Hofstra University-Northshore Long Island Jewish	Acharya/Bakar/Lau
Boston Children's Hospital (Boston, MA)	Harvard University	Kumar/Randolph
Akron Children's Hospital	Northeast Ohio Medical University	Fargo/McKee/Rajbhandari
Children's of Alabama	University of Alabama Birmingham	Wilson/Hallman/Molina
Children's Hospital of Atlanta	Emory University	Woods/Hebbar
Children's Hospital of Pittsburgh	University of Pittsburgh	Xavier/Aneha
Children's National Medical Center	George Washington University	Diab/Siems/Pavuluri

Alternate/Supplemental Centers

Site Name (Location)	Affiliation	PI /Sub-I(s)
Johns Hopkins Children's Center (Baltimore, MD)	Johns Hopkins University	Lawrence/Kudchadkar
Cincinnati Children's Hospital (Cincinnati, OH)	University of Cincinnati	Tarango/Chima/Jerardi
Children's Hospital of New Orleans (New Orleans, LA) ¹	Louisiana State University	Godiwala/Palombo/Prasad
Children's Hospital of Michigan	Wayne State University	Rajpurkar/Bauerfeld
Lurie Children's Hospital	Northwestern University	Bhat/Barhight/Harris

Appendix 2. Clinical Coordinating Center description of responsibilities.

Johns Hopkins All Children's Hospital will serve as the Clinical Coordinating Center for the study entitled "COVID-19 Anticoagulation in Children - Thromboprophylaxis (COVAC-TP) Trial". The Clinical Coordinating Center for Pediatric Multicenter Studies at JHACH provides Principal Investigators (PIs) with the infrastructure to successfully lead and conduct multicenter pediatric studies. This is accomplished by leveraging the existing resources within the JHAC Clinical and Translational Research Organization (CTRO) and All Children's Research Institute (ACRI) and applying them to the overall management and organization of a multicenter study.

Led by a team of Project Managers (PMs), the CCC manages the project through each phase of the study lifecycle from start-up through close out and manuscript publication.

- In collaboration with the PI, PMs develop and revise all study documents including the protocol, consent, and operations manuals and communicates any changes to the participating sites.
- PMs assist the Principal Investigator (PI) in selecting highly-reliable sites with a proven track-record of accrual and compliance.
- PMs maintain contact information for each site.
- PMs maintain CCC IRB approvals and approved consents (local, single, or central) as well as on an ongoing basis the study's overall Trial Master File (TMF) of regulatory documents.
- PMs confirm that each participating center has an FWA on file with OHRP.
- PMs provide training to site staff at initiation as well as ongoing through monthly conference calls and webinars as well as annual investigator meetings.
- In collaboration with the PI and study biostatistician, the PM develops and tests Case Report Forms (CRFs).
- In collaboration with the JHAC CTRO Regulatory Affairs/Quality Assurance Unit, PMs perform remote monitoring of participating site's regulatory documentation and study data to ensure data accuracy, completeness and integrity.
- PMs facilitate the reporting of problem events from participating sites.
- Coordinates with the JHAC Pediatric Biorepository to design, prepare and ship kits for sample collection, receipt, and to coordinate return shipment, receipt and storage of biological samples, with accompanying sample tracking information.