Data Coordinating Center for Pediatric Multicenter Studies
Institute for Clinical and Translational Research
601 5th Street South, Suite 711
St. Petersburg, FL 33701
HopkinsAllChildrens.org

Trial monitoring plan – NCT04354155

STATISTICAL ANALYSIS PLAN

PROJECT TITLE:	COVID-19 Anticoagulation in Children - Thromboprophylaxis (COVAC-TP) Trial
PRINCIPAL INVESTIGATOR:	Anthony Sochet, MD, MPH
DEPARTMENT/INSTITUTE:	Clinical and Translational Research Institute
INSTITUTION:	Johns Hopkins All Children's Hospital
SAP DATE:	July 14, 2021
DATA SOURCE:	Redcap
PREPARED BY:	Ernest Amankwah, PhD

SAP History:

Version Number	Version Date	Summary of Revisions Made:
1.00	7-Apr-20	Initial
1.01	14-Jul-21	To present results by age and MISC status

Table of Contents

1. STUDY OBJECTIVES

1.1. SPECIFIC AIM 1

- To investigate the safety of in-hospital thromboprophylaxis with twice-daily low-dose enoxaparin thromboprophylaxis (starting dose, 0.5 m/gkg 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).

1.2. 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).

1.3. SPECIFIC AIM 3

- 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 (<2x 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).

2. STUDY DESIGN

The study is a phase 2, single-arm, open-label, non-randomized clinical trial conducted at 12 centers in the US 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 (MISC)

2.2. TREATMENT GROUPS

One

2.3. STUDY POPULATION

Inclusion Criteria

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 MIS-C Patients Who Do Not Already Meet the Above Criteria for COVID-Infected Patients:

1. 1. Children (birth to <18 years of age)
2. 2. Signs and symptoms of COVID-19 Multi-System Inflammatory Syndrome (MIS-C) including: i.) fever ≥ 3 days;
3. ii.) Two or more of the following: a) Rash of bilateral non-purulent conjunctivitis or muco-cutaneous inflammation (oral, hands, or feet),
4. b) Hypotension or shock,
5. c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP),
6. d) Evidence of coagulopathy (by PT, PTT, or d-Dimer)
7. e) Acute gastrointestinal problems (diarrhea, vomiting, abdominal pain)
8.
9. iii.) Elevated markers of inflammation (erythrocyte sedimentation rate, C-reactive protein, or pro-calcitonin);
10. iv.) No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndrome;
11. v.) Known exposure to a SARS-CoV-2 positive case, as documented by clinical history

Exclusion Criteria

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/μL within the past 24 hours
6) Prothrombin time (PT) ≥2 seconds above the upper limit of age-appropriate local reference range within the past 24 hours
7) Activated partial thromboplastin time (aPTT) ≥4 seconds above the upper limit of age-appropriate local reference range within the past 24 hours
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.

2.4. EXPOSURE

Enoxaparin dose

2.5. SAMPLE SIZE

The study enrolled 38 participants

3. OUTCOME VARIABLES

3.1. PRIMARY OUTCOME(S)

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

3.2. SECONDARY OUTCOMES

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.

3.3. EXPLORATORY OUTCOMES

Proportion of plasma D-dimer levels <2x ULN; cumulative incidence of VTE; and duration of assisted ventilation (Mechanical ventilation, Non-invasive ventilation and Extracorporeal life support).

3.3. OTHER PARAMETERS

3.3.1 Demographic and clinical characteristics

- Age, median years
- Gender
- Weight
- BMI
- Complete blood count
  - White blood count
  - Hemoglobin
  -Platelet

-Coagulation

-Prothrombin time

-Partial thromboplastin time

-International normalized ratio

-Fibronogen

-D-dimer

-Creatinine

3.3.2 Clinical measures

-COVID-19-related medications

-Corticosteroids

-Nonsteroidal anti-inflammatory

-Intravenous immunoglobulin

-Remdesivir

-Azithromycin

-Anakinra

- Tocilizumab

- Hospital course

- Length of stay

-Mortality

-Central venous catheterization

- Discharged on thromboprophylaxis

- Discharged on aspirin

4. STATISTICAL METHODOLOGY

4.1. GENERAL METHODOLOGY

Data analysis for this study will be performed at the JHAC DCC-PMCS at study completion, once the database has been locked and the Statistical Analysis Plan has been finalized and approved by the study team.

4.1.1. Population for analysis

The population will include all enrolled patients who: 1) had no protocol violations in eligibility criteria; 2) received at least one dose of enoxaparin; and 3) underwent primary outcome determination within 30 days of COVID diagnosis.

4.1.2. Baseline data

The flow of patients, including the overall eligible patients, excluded patients and patients in the analytic dataset will be presented in a Figure (Figure 1). We will present demographic and clinical characteristics for all patients and by age (<12 and >=12 years) and MISC status (Table 1). Continuous variables will be summarized as means with standard deviations or medians with observed range or interquartile range and compared between groups with independent t-test or Mann-Whitney U test as appropriate. Categorical variables will be summarized as counts with percentages and compared using the Chi-squared test or Fishers exact test as appropriate. All statistical analyses will be performed with SAS v 9.4

4.1.3. Distributional assumptions

- The distribution of continuous variables will be evaluated for normality.

4.1.4. Handling of missing data

The analysis for all the Aims will be a complete case analysis. Missing data will not be imputed.

4.1.5. Protocol violations and patient withdrawals

All deviations / violations to the protocol (if applicable) will be summarized using counts and frequencies. Similarly, reasons for early withdrawal from the study will be summarized using counts and frequencies.

4.2. ANALYSIS OF THE PRIMARY OUTCOME

The primary endpoint, cumulative incidence of ISTH-defined clinically-relevant bleeding events during hospitalization, will be calculated with the corresponding exact (Clopper-Pearson) 90% confidence intervals (90%CIs)

4.3. ANALYSIS OF THE SECONDARY OUTCOME

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 and MISC status. Distributions will be compared across groups, if there are adequate numbers in the groups, using Mann-Whitney U test.

4.4. ANALYSIS OF THE TERTIARY OUTCOMES

The tertiary outcomes will be calculated as proportions and cumulative incidences with 90%CIs, and medians with IQRs for all the study participants combined and by age group and MISC status

4.5 STUDY POWER

With a sample size of 38 patients in the safety population, the precision of estimates for various cumulative incidences of clinically-relevant bleeding (with corresponding 90% CIs) was as follows: 0/38, 0% (0-7.6%); 1/38, 2.6% (0-11.8%); 2/38, 5.3% (0-15.7%).