Trial Protocol

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1. INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in Wuhan, China, on 31 December 2019. The World Health Organization (WHO) declared the outbreak a global health emergency on 30 January 2020. The infection can be transmitted by direct interpersonal contact, fomites, respiratory secretions, and direct viral shedding into the air via normal respiration. SARS-CoV-2 has been isolated from both feces and urine.

From the beginning of the month to April 15, 2020 New York State has reported over 203,377 cases of SARS-CoV-2 infection and 10,834 deaths. New York City has reported over 107,263 cases of SARS-CoV-2 infection and 10,367 deaths

Recent data is emerging of a very high incidence of thromboembolic complications, especially venous thromboembolic (VTE) complications, in hospitalized COVID-19 patients, especially the sick hospitalized patients in Intensive Care Units (ICU) with respiratory failure. Although hospital and antithrombotic guidelines advocate for routine VTE risk assessment and use of standard thromboprophylaxis, recent reports also suggest the failure to prevent thromboembolic events in these patients using standard or routine thromboprophylaxis strategies, likely due to the prothrombotic state seen in these patients. Previous data suggests a mortality advantage in using empiric treatment dose anticoagulant therapy with heparin in patients with severe viral pneumonia.

To date, there is no data to inform the optimal dose of heparin thromboprophylaxis in the sick, hospitalized, and likely prothrombotic COVID-19 population. Multiple international antithrombotic societies have advocated high quality data to inform this critical clinical question, and to definitively answer the question of whether empiric treatment dose heparin therapy confers a net clinical benefit to reduce major thromboembolic events and associated mortality in this population.
1.1. Background

COVID-19 patients have been noted to have significantly elevated markers of hypercoagulability including d-dimer (Dd), fibrinogen levels, FVIII levels, short activated partial thromboplastin time (aPTT) and Sepsis-Induced Coagulopathy (SIC) scores with an increase in venous thromboembolic disease as well as cardiac injury, for which potential causes may include atherothrombosis, demand ischemia or microthrombosis. The mechanism underlying morbidity related to thrombosis in COVID-19 patients remains unclear (1).

There are clinical data to support the observation that hospitalized acutely ill medical patients with severe viral pneumonitis/Acute Respiratory Distress Syndrome (ARDS), such as those with influenza H1N1 infection, have an over 23-fold increased risk for venous thromboembolism (VTE) - especially pulmonary embolism (PE) - with an overall 44% incidence of VTE in ARDS associated with H1N1 pneumonia (2). Multicenter studies from China report that key markers of inflammation and/or coagulopathy are associated with morbidity and increased mortality in COVID-19 patients. Elevated D-dimer levels (that are sometime greater than 4 or 6 times the upper limit of normal [ULN]) are strongly associated with mortality in patients with severe COVID-19 illness (3,4). Recent data also shows that mortality among COVID-19 patients is markedly higher in patients with elevated TnT levels than in patients with normal TnT levels (5). Recently, Cui and colleagues retrospectively evaluated a cohort of 81 patients diagnosed with severe COVID-19 pneumonia and reported a lower extremity VTE incidence of 25% (20/81) and a mortality of 40% (8/20) in the presence of VTE (6). Danzi et al reported a case of bilateral pulmonary embolism in a 75 year old woman diagnosed with severe COVID-19, in the absence of predisposing risk factors and a negative lower extremity US (7). Lastly Wang et al investigated the use of Tissue Plasminogen Activator (tPA) in the treatment of COVID-19 associated ARDS and reported promising, but transient, results in terms of pulmonary function improvement (8). It appears that either the SARS-CoV2 infection itself induces a hypercoagulable state, possibly by hypofibrinolytic mechanisms, or the cytokine storm in COVID-19 patients with severe disease induces a prothrombotic state, which leads to clinical deterioration, hypoxia and hemodynamic instability secondary to thromboembolic phenomena and potentially cardiac ischemia (9). Preliminary data from Northwell Health System, which has one of the largest populations of hospitalized COVID-19 patients in the US, reveals a positivity rate for deep vein thrombosis (DVT) of 40% of those COVID-19 patients screened by Doppler compression ultrasonography of the lower extremities (internal Northwell data).

Heparin has been shown to have anti-inflammatory and immunomodulatory properties in addition to its anticoagulation effect, which could play a beneficial role in sepsis (10). In addition, there is in vitro evidence that the large negatively charged sulfated glycosaminoglycans of unfractionated heparin may act as an alternate ligand for the SARS-CoV2 receptor irrespective of ACE2 (4). Whether this in vitro evidence supports the role of a protective or deleterious mechanism in COVID-19 infection is not known. However, an early report with empiric use of treatment dose unfractionated heparin (UFH) in ARDS from a different viral family, influenza H1N1, revealed that H1N1 ARDS patients under systemic anticoagulation had 33-fold fewer VTE events than those treated given prophylactic doses of UFH/low-molecular weight heparin (LMWH) thromboprophylaxis (2). Very recent evidence suggests that therapy with prophylactic to intermediate doses of the LMWH enoxaparin (30mg to 60mg QD) in severe hospitalized COVID-19 patents with a SIC score ≥ 4 or D-dimer (Dd) > 6 X ULN improves outcomes and prognosis (4). All-cause mortality at 28 days was reduced from 64.2% to 40.0% in those patients with a SIC score > 4 (p=0.029).
and from 52.4% to 32.8% in those patients with an elevated Dd > 6 x ULN (P=0.017) (4). Notably, Klok and colleagues investigated 184 ICU patients infected with COVID-19 and reported a 13% mortality rate, a relatively high incidence of CTPA- or ultrasonography-confirmed VTE rate (27%), and arterial thrombotic events (3.7%) despite the use of standard dose thromboprophylaxis (11). Postulated mechanisms for the improved prognosis with the use of treatment doses of LMWH in the sick COVID-19 population include the decrease in the risk of microthrombi, especially in the pulmonary vasculature, which can lead to hypoxemia, pulmonary vasoconstriction and right ventricular dysfunction as well as the decrease in the risk of progression to disseminated intravascular coagulopathy as a contributor to the high mortality seen in these patients (12).

1.1.1. Pharmaceutical and Therapeutic Background

The optimal dose of heparin (either LMWH or UFH) in hospitalized COVID-19 patients is unknown, as patients on conventional prophylactic dose heparin (UFH or LMWH) as supported by international guidance statements on hospitalized COVID-19 patients appear to remain at risk for thromboembolic events (13). There is data to support improved efficacy with treatment doses of twice daily enoxaparin versus once-daily weight-adjusted enoxaparin for the management of VTE, especially with large thrombus burden (14). There is also long-standing data to support that treatment-dose heparin can reduce major cardiovascular events (15). Our current standard of care in our 24 hospital Northwell Health System, which has a very large hospitalized COVID-19 patient population, is to use Lovenox 40mg SQ QD for patients with a BMI < 30 and Creatinine Clearance (CrCl) > 15ml/min, Lovenox 40mg SQ BID for patients with a BMI > 30 and CrCl > 15ml/min, and UFH 5000U SQ BID or TID in patients with a CrCl < 15ml/min and BMI < 30 and UFH 7500U SQ BID or TID with a CrCl < 15ml/min and BMI > 30. (Appendix A). The aim of this study is to test the hypothesis that prophylaxis of severe COVID-19 patients with treatment dose LMWH leads to better thromboembolic-free outcomes and associated complications during hospitalization than prophylaxis with our institution’s current standard of care with prophylactic to intermediate-doses of LMWH.
1.2. Study Rationale

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives
Our hypothesis is that sick hospitalized COVID-19 patients receiving therapeutic doses of heparin (LMWH) during hospitalization will show a reduction of the primary and secondary endpoints that are associated with a prothrombotic state within 30 days of their hospital admission.

2.1.1. Primary Objective
The overall objective of the study is to evaluate the clinical efficacy of therapeutic low molecular weight heparin (LMWH) versus prophylactic/intermediate doses of LMWH as per our institution’s protocols in reducing the composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Day 30 ± 2 days.

2.1.2. Secondary Objectives
To evaluate the safety of such an approach by assessing the risk of major bleeding defined using the International Society of Thrombosis and Haemostasis (ISTH) criteria at Day 30 ± 2 days.
2.2. Hypothesis

Patients receiving therapeutic doses of heparin (LMWH) patients will show a reduction of the primary and secondary endpoints that are associated with a prothrombotic state within 30 ± 2 days of their hospital admission.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoints

Primary Clinical Endpoint: The composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Day 30 ± 2 days.

1. Any arterial thromboembolic event defined by:
   a. Documented thromboembolic stroke by imaging (Head CT, Brain MRI) defined as a new focal neurologic defect lasting at least 24 hours that is not due to a readily identifiable non-vascular cause
   b. Documented peripheral arterial thromboembolism by imaging (CT scan, arteriography, arterial Doppler of extremities)
   c. Documented acute myocardial infarction defined by 2 of the 3 following conditions: 1) an appropriate clinical condition such as new EKG changes, 2) elevation of CK-MB or Troponin-T or I ≥ 2 X ULN (if CK-MB or troponin unavailable then total CK ≥ 2 X ULN), 3) new significant (≥0.04 seconds) Q waves in ≥ two contiguous leads

2. Any new venous thromboembolic event (symptomatic DVT or asymptomatic proximal DVT found by screening ultrasonography or as an incidental finding of PE on CT scan) including DVT of upper or lower extremities, PE, splanchnic vein thrombosis, cerebral vein thrombosis defined by:
   a. One or more new filing defects at compression ultrasonography, venography, CT venography, or MR venography
   b. A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion scan (V/Q scan)

3. All-cause mortality
**Principal Safety-endpoint:** Major bleeding using ISTH criteria at 30 ± 2 days.

1. Documented major bleeding using ISTH criteria defined by:
   a. A decrease in hemoglobin of 2g/dl or more within 24 hours
   b. A transfusion of 2 or more units of packed red blood cells
   c. Critical site bleeding (including intracranial, intraocular, intra-articular, retroperitoneal, intramuscular with component syndrome, pericardial)
   d. Bleeding that is fatal
   e. Bleeding that necessitates surgical intervention

2.3.2. **Secondary Efficacy Endpoint**

The composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Hospital Day 10 + 4

Sepsis-induced coagulopathy (SIC) score, ISTH DIC score, progression to Acute Respiratory Distress Syndrome (ARDS), need for intubation, re-hospitalization at Day 30 ± 2 days.
3. STUDY DESIGN

3.1. Overall Design

Prospective Open-label Randomized Trial using an Active Control Group, with patients stratified by ICU stay or Non-ICU stay
3.1.1. Study Duration
The study is expected to last for up to six months.

3.1.2. Duration of Study Participation
An individual subject will complete the study in about 30 ± 2 days, from screening at Day -1 or 1 to follow-up visit on Day 30 ± 2 days. If a participant is unable to return to the site for Day 30±2 assessment, safety will be assessed via Telemedicine or telephone contact.

4. STUDY POPULATION

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

4.1.1.1. Inclusion Criteria for Study Subjects
1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
4. Subject consents to randomization within 72 hours of hospital admission.
5. Subjects with a positive COVID-19 diagnosis by nasal swab or serologic testing
6. Hospitalized with a respiratory rate > 20 and an oxygen saturation < 92% on room air
7. Have:
   • Either a D- Dimer > 6.0 X ULN OR
   • Sepsis-induced coagulopathy (SIC) score of ≥4
4.1.2. Exclusion Criteria

1. Indications for therapeutic anticoagulation

2. Absolute contraindication to anticoagulation including:

   a. active bleeding,
   b. recent (within 1 month) history of bleed,
   c. dual (but not single) antiplatelet therapy,
   d. active gastrointestinal and intracranial cancer,
   e. a history of bronchiectasis or pulmonary cavitation,
   f. an IMPROVE Bleed score of ≥ 7 ([Appendix C]),
   g. CrCl < 15ml/min,
   h. a platelet count < 25,000,
   i. a history of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies.
   j. contraindications to enoxaparin including a hypersensitivity to enoxaparin sodium, hypersensitivity to heparin or pork products, hypersensitivity to benzyl alcohol
   k. pregnant females
   l. inability to give or designate to give informed consent
   m. participation in another blinded trial of investigational drug therapy for COVID-19 ([Applies to both Study Subjects and Randomized Subjects])

4.1.2.1. Rationale for Selected Exclusion Criteria

LMWH has a well-established risk of clinically important bleeding, including major and fatal bleeding, with therapeutic doses of drug increasing this risk. The clinical exclusionary criteria as established by previous randomized trials of anticoagulant therapy in patients with thrombotic disorders and as used by the Hep-COVID trial represent well-established high clinical bleed risk factors. The IMPROVE Bleed risk model, with a cut off of 7 or more, has also been validated in hospitalized medical ill patients to identify a high bleed risk population. Pregnant women will be excluded due to uncertain characterization of the risk of VTE when hospitalized with COVID-19 with unlikley net clinical benefit from an aggressive thromboprophylactic strategy.
5. STUDY TREATMENTS

5.1. Assigning Randomized Subjects to Treatments

5.1.1. Stratification
Prior to randomization, subjects will be stratified according to whether they are in a designated ICU unit or not.

5.1.2. Randomization
This study is a randomized, controlled trial using open-label active controls to evaluate the efficacy and safety of treatment dose LMWH versus prophylactic/intermediate dose LMWH in sick hospitalized adult patients diagnosed with COVID-19 during their hospitalization. The study is a multi-site trial that will be conducted in hospitals within the Northwell Health system in New York, United States. The study will compare the following two active treatment arms that patients received during their hospitalization:

Arm 0: Enoxaparin 1mg/kg SQ BID for CrCl ≥ 30ml/min (or Enoxaparin 0.5mg/kg SQ BID for CrCl ≥ 15ml/min and < 30ml/min) during the course of their hospitalization

Arm 1: Enoxaparin 40mg SQ QD for CrCl ≥ 15ml/min and BMI < 30 and Enoxaparin 40mg SQ BID for CrCl ≥ 15ml/min and BMI ≥ 30 during the course of their hospitalization

Randomization into Arms 0 and 1 will be carried out using a balanced 1:1 design.

The Biostatistics Unit will develop and implement the randomization procedure using the Biostatistics Randomization Management System (BRMS). The Biostatistics Randomization Management System (BRMS) is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using their personal computer. The BRMS allows for multi-center, stratified, and single/double blinded RCTs, using permuted blocks. Randomization notifications (respectful of blinding status) are automatically sent to the PI and other authorized personnel. BRMS includes a feature that allows for medically indicated breaking of the blind, with requirement for justification. BRMS includes an audit trail of all transactions.
5.2. Study Drug
Enoxaparin injection, in vials

5.2.1. Description
Enoxaparin injection is an anticoagulant medication approved for use to prevent thromboembolic complications. Both doses as per as protocol are approved for use in hospitalized patients.

5.2.2. Preparation
Enoxaparin injection is available in pre-filled syringes in 40mg, 60mg, 80mg, 100mg, 120mg, or 150mg vials.

5.2.3 Administration
Enoxaparin injection will be administered at a dose of 1mg/kg SQ BID, or a dose of 40mg SQ QD for patients with a BMI < 30 or or 40mg SQ BID for patients with a BMI ≥30. Patients will have study drug administered for the duration of their hospitalization.

5.2.4 Storage

Enoxaparin injections can be stored at room temperature.
5.2.3. **Pregnancy**
Pregnant females are excluded from the present study.

5.2.4. **Contraception**
Women of childbearing age must agree to use contraception for the duration of study treatment prior to providing consent.

5.2.7 **Adverse Reactions**
Heparin (LMWH) including enoxaparin is usually well tolerated; most adverse reactions have been mild and transient. Some common adverse reactions include: anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, nausea, fever, edema, peripheral edema, dyspnea, bleeding gums, nosebleeds, prolonged bleeding from cuts, confusion and injection site pain. There is an unlikely risk of serious allergic reactions with Enoxaparin. In some cases there have been reports of spinal/epidural hematomas in patients receiving neuraxial anesthesia or undergoing spinal puncture.

5.4. **Drug Accountability**
All drug accountability records will be kept current and contain the dates, quantity, and study medication dispensed to each subject. The PI must be able to account for all opened and unopened study drug. All unused study drug must be disposed of at the site or returned to the sponsor or designee. All drug accountability records will be made available for inspection by regulatory agencies, and kept on file onsite as per Northwell Health institutional policy.

5.5. **Guidelines for Delay, Reduction and/or Discontinuation of Study Medications**
Dose modification for an individual subject is not permitted. If a subject requires modification or discontinuation of study medication they will be withdrawn from the study and standard of care treatment will be initiated.

5.6. **Prior and Concomitant Medications**
Concomitant use of hepatotoxic medications, immunosuppressive therapy and/or investigational study drugs for the treatment of COVID-19 with the exception of blinded investigational therapies for COVID-19 are permitted as per usual standard of care. Any other treatment administered from the first dose of study drug to the final study assessment will be considered concomitant medication and recorded per subject.

5.7. **Method of Assessing Treatment Compliance**
Study drugs will be administered per protocol while subjects are hospitalized. Medication records will be made available for inspection by the sponsor and/or regulatory agencies, and kept on file onsite as per Northwell Health institutional policy.

5.8. **Subject Withdrawal/Discontinuation**
A subject has the right to withdraw from the study at any time. The investigator and/or sponsor have the right to withdraw a subject from the study if it is no longer in the best interest of the subject to continue, or if the subject’s continuation in the study places the scientific outcome of the study at risk.

5.8.1. Subject Replacement
Due to the large target enrollment and short treatment duration of this study, withdrawn subjects will not be replaced.
6. STUDY PROCEDURES (applied to concurrent randomized subjects only)

6.1. Screening

Upon admission, the research coordinator will be notified about potentially eligible patients who require screening. The lab parameters required to determine eligibility are part of standard of care and will be available to the research coordinator shortly after admission. There will be an up to a 72 hour window from admission by which to randomize patients into the trial.

6.2. Enrollment

Upon meeting the inclusion/exclusion criteria including consent, the research coordinator will officially enroll the subject and implement the randomization procedure.

6.3. Treatment Period

Treatment with study medication enoxaparin will be for the duration of hospitalization.

In the post-hospital discharge period, patients will receive either enoxaparin 40mg SQ QD or rivaroxaban 10mg PO QD for up to 39 days as per usual care using our institution’s anticoagulation protocol at the discretion of the investigator (Appendix A). However, other antithrombotic therapy, including low dose aspirin, is permitted, although discouraged.

No additional research procedures are indicated.

6.4. Follow-up

Subjects will be followed at Hospital Day 10 + 4, and for Day 30 ± 2.

7. EFFICACY ASSESSMENTS

At Hospital Day 10 + 4 or sooner at the time of hospital discharge, there will be a lower extremity Duplex screening compression ultrasonography using standardized screening methods. Confirmatory lower extremity ultrasound of symptomatic DVT or asymptomatic screening of lower extremity DVT is recommended using full duplex Doppler compression ultrasonography of the entire extremity venous system. Where resource constraints or local institutional policies preclude use of full ultrasound, point-of-care ultrasound using two-region compression can be substituted and has shown reasonable accuracy. There will also be an assessment of the primary efficacy, principal safety, and secondary outcomes.

At Day 30 ± 2, there will be an assessment of the primary efficacy, principal safety, and secondary outcomes via a face-to-face or telephonic visit.
8. SAFETY EVALUATION AND REPORTING

8.1. Assessment of Safety Endpoints
Subject safety will be assessed continuously while hospitalized as per standard of care for hospitalized patients. Upon discharge, subject safety will be assessed at a follow up visit on Day 30 ±2. Subjects unable to return will be assessed via Telemedicine or by telephone.

8.2. Adverse Events and Serious Adverse Events

8.2.1 Definition of Adverse Event (AE)
Adverse event is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.2.2. Definition of Serious Adverse Event (SAE)
An adverse event (AE) or suspected adverse reaction 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. 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.3. Classification of Adverse Event

8.2.3.1. Severity of Event

The following guidelines will be used to describe severity of Adverse Events (AE):

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.2.3.2. Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
• **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).

• **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

### 8.2.3.3. Expectedness

The DSMB will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### 8.2.4. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded. Events will be followed for outcome information until resolution or stabilization.

### 8.2.5. Adverse Event Reporting

Adverse events (AE) will be reported immediately to the PI and the Co-Investigators. It will also be reported to the Northwell IRB and to all members of the research team.

### 8.2.6. Serious Adverse Event Reporting
The study clinician will immediately report any serious adverse event (SAE), whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event will be recorded.

The Principal Investigator (PI) will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after initial receipt of the information.

8.2.7. Reporting Events to Participants
Participants will not be informed of AEs and SAEs unless the AE or SAE happened to them.

8.2.8. Events of Special Interest
N/A

8.2.9. Reporting of Pregnancy
N/A

8.3. Unanticipated Problems

8.3.1. Definition of Unanticipated Problems (UP)
The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2. Unanticipated Problem Reporting
The investigator or study team member who becomes aware will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Principal Investigator (PI). The UP report will include the following information:
8.4. Other Safety

8.4.1. Clinical Laboratory Evaluations

Laboratory values will be obtained by venipuncture and evaluated on the day of randomization:

1. PT/INR (standard of care)
2. Platelet count (standard of care)
3. Hemoglobin/hematocrit (standard of care)
4. Serum creatinine (standard of care)
5. D-dimer (allowed within 72 hours prior to randomization) (standard of care)
6. C-reactive protein (CRP) (allowed within 72 hours prior to randomization) (standard of care)
7. Fibrinogen (allowed within 72 hours prior to randomization) (standard of care)
8. Troponin (allowed within 72 hours prior to randomization) (standard of care)
9. Antiphospholipid studies (lupus anticoagulant by dilute Russel Viper Venom Study and Silica Clotting Time, anticardiolipin antibodies, b2glycoprotein antibodies) (allowed within 72 hours prior to randomization) (research purposes)
10. Protein C antigen/activity and Protein S Antigen/activity (allowed within 72 hours prior to randomization) (research purposes)
11. Antithrombin activity (allowed within 72 hours prior to randomization) (research purposes)
12. Quick SOFA score (Appendix D) (allowed within 72 hours prior to randomization)
13. ISTH SIC score (Appendix B) (allowed within 72 hours prior to randomization)
14. IMPROVE VTE score (Appendix E) (allowed within 72 hours prior to randomization)
15. Medical History (including comorbid conditions such as congestive heart failure, diabetes mellitus, a history of cardiovascular disease including venous thromboembolism and peripheral
vascular disease, history of atrial fibrillation, known thrombophilia, history of hypertension, a history of dyslipidemia, a history of coronary artery disease or congestive heart failure, a history of renal or lung disease, a history of liver disease, a history of thyroid disease, a history of cancer, a history of autoimmune disease, a history of bleeding diathesis, recent surgery or trauma, tobacco use)

18. Relevant medications (all antiplatelet agents such as aspirin, clopidogrel, ticagrelor, prasugrel, vorapaxar, cangrelor; thrombolytic agents such as tPA; steroids; use of chloroquine or hydroxychloroquine; hormonal therapy; use of famotidine, immunosuppressants or immunomodulatory agents, antivirals, non-steroidal anti-inflammatory agents).

19. Use of IVC filter

20. Mechanical thromboprophylaxis (intermittent pneumatic compression devices, graduated compression stockings)

After randomization, the following data will be captured and collected as per trial protocol on Hospital Day 10 + 4 or at the time of discharge, whichever comes first:

1. PT/INR (standard of care)
2. Platelet count (standard of care)
3. Hemoglobin/hematocrit (standard of care)
4. Serum creatinine (standard of care)
5. D-dimer (standard of care)
6. C-reactive protein (CRP) (research purposes)
7. Fibrinogen (research purposes)
8. Troponin (research purposes)
9. Quick SOFA score (Appendix D)
10. ISTH SIC score (Appendix B)
11. IMPROVE VTE score (Appendix E)
12. Relevant medications (all antiplatelet agents such as aspirin, clopidogrel, ticagrelor, prasugrel, vorapaxar, cangrelor; thrombolytic agents such as tPA; steroids; use of chloroquine or hydroxychloroquine; hormonal therapy; use of famotidine, immunosuppressants or immunomodulatory agents, antivirals, non-steroidal anti-inflammatory agents).
13. Use of IVC filter
14. Mechanical thromboprophylaxis (intermittent pneumatic compression devices, graduated compression stockings)

8.4.2. Vital Signs
Vital signs will be collected daily as per the standard of care for hospitalized patients.

8.4.3. Physical Examination
Changes in clinical severity will be assessed via physical examinations.

8.4.4. Other Examinations
Lower extremity Duplex screening compression ultrasonography will be done at Hospital Day 10±4 or sooner at the time of hospital discharge using standardized screening methods.

There will be a 30 ± 2 days day face to face or telephonic visit to assess study outcomes including the primary efficacy and principal safety outcomes or adverse events

Patients will be on standard medical therapy for COVID 19 as per our institutional guidelines and policies. Patients participating in another clinical trial of blinded investigational drug therapies for COVID-19 will be excluded. The management of adverse events such as heparin-induced thrombocytopenia, an arterial or venous thromboembolic event, or major or critical site bleeding event will be as per usual medical care. There is guidance to suggest that a dose increase of LMWH by 25% is acceptable to treat refractory thrombosis despite adequate weight adjusted treatment doses of LMWH (17,18). For patients that need temporary interruption of study medication for an invasive procedure or surgery, investigators will follow local established guidelines for both doses of enoxaparin. If a patient develops severe renal failure with a CrCl < 15ml/min during the course of their hospitalization, their study medication will be switched to intravenous or subcutaneous unfractionated heparin as per usual care using our institutional guidelines (Appendix A).

For patients with rising troponins and electrocardiographic changes that reflect standard definitions of NSTEMI recommendations will be made to start aspirin regardless of heparin dose.

Other examinations may include nasopharyngeal swabs to analyze virologic clearance per standard of care for COVID-19 patients.

Additional SOC examinations performed during the inpatient treatment period will be documented in the subject file and reviewed to assess safety.

9. STATISTICAL METHODS

9.1. General Statistical Considerations

The primary clinical objective is to compare the incidence of the primary safety and efficacy outcomes, and secondary outcomes at Day 30 ± 2 days between patients receiving full dose LMWH treatment and patients receiving prophylactic/intermediate dose LMWH. A key secondary endpoint to compare the incidence of the primary safety and efficacy outcomes, and secondary outcomes at Hospital Day 10 ± 4.

9.2. Analysis Sets

Assuming a 40% relative risk reduction in the primary efficacy outcome with LMWH treatment (4) and an incidence of the primary efficacy endpoint of 42% in the usual medical care arm (2, 4, internal Northwell data), 246 patients will be needed to be enrolled (123 in each arm) to have 80% power
with a two-sided significance level of 0.05. Assuming a 20% drop out rate, we will need 308 patients in total. The primary analysis will be done in the per-protocol population. The per protocol analysis set will consist of all patients who received at least 80% of planned therapy. The safety analysis will consist of all patients who received at least one dose of study medication. There will be a single interim analysis as described below.

Under the design assumptions with 246 patients, therapeutic dose treatment with LMWH treatment will be deemed to be superior to prophylactic/intermediate dose treatment (i.e., 2-sided $p < 0.05$) if upon trial completion the absolute risk reduction with therapeutic LMWH group is -0.117 (11.7%) lower than in the prophylactic/intermediate dose group. A single interim analysis is planned after the primary outcome status is observed on half (123) of the randomized patients. The interim analysis will allow early termination for evidence of efficacy if the absolute risk reduction (ARR) is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate dose group. Table 1 shows the statistical inference that would be reported if the trial stops at the critical value (15 fewer events) at both the interim and final analyses. Table 2 shows the statistical operating characteristics of the design.

**Table 1**: Statistical inference upon trial completion.

<table>
<thead>
<tr>
<th></th>
<th>Efficacy Decision</th>
<th>Futility Decision</th>
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<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>CIlo</td>
</tr>
<tr>
<td><strong>Interim Analysis</strong></td>
<td>-0.234</td>
<td>(-0.338, -0.068)</td>
</tr>
<tr>
<td><strong>Final Analysis</strong></td>
<td>-0.117</td>
<td>(-0.234, 0.000)</td>
</tr>
</tbody>
</table>

For example, the trial will stop for efficacy at the interim analysis if the ARR is smaller than -0.234 (23.4% reduction in risk of the primary efficacy event. The trial will stop for futility if the risk of and event is larger with therapeutic dosing than with prophylactic dosing. The study will continue to the final analysis if the observed ARR is between -0.234 and 0.000. At the final analysis superiority is decided (1-sided $p<0.025$) if the observed ARR is smaller than -0.0117. The confidence intervals and p-values show the result that would be reported (e.g., the hypotheses that would be ruled out) if the observed ARR was equal to the decision boundary. For example, if the observed ARR equals -0.234 at the interim analysis, then the 95% confidence rules out reductions smaller than 33.8% or larger than 6.8% with 1-sided $p=0.0027$. 

Table 2: Statistical operating characteristics of the design.
Table 2: Statistical properties of the interim monitoring design.

<table>
<thead>
<tr>
<th>True treatment effect</th>
<th>Statistical properties of the design</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Power</td>
</tr>
<tr>
<td>P1</td>
<td>ARR</td>
</tr>
<tr>
<td>0.252</td>
<td>-0.168</td>
</tr>
<tr>
<td>0.210</td>
<td>-0.210</td>
</tr>
<tr>
<td>0.168</td>
<td>-0.252</td>
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</table>

The statistical properties of the interim analysis design include the power the average sample size of trials that are monitored using this design and the probability of stopping at the interim analysis. These properties are a function of the true treatment effect; specifically, ARR = -0.168, ARR = -0.210, and ARR = -0.252 denotes a relative risk of 60%, 50%, and 40% of therapeutic dose relative to prophylactic dose (risk = 0.42); e.g. P1= 0.252 = 0.42*0.6 so ARR = 0.252 - 0.420 = -0.168

9.3. Efficacy Analyses

9.3.1. Summaries of Baseline Demographic and Clinical Data

All baseline demographics and clinical data will be summarized by treatment arm using frequencies, rates, means, medians, standard deviations and quartiles appropriate to the dataset. There will be no inferential comparison of treatment arms with respect to baseline and demographic clinical data; such comparisons will be descriptive only. Unless otherwise specified, all results will be considered significant if p<0.05.

9.3.2. Comparability of Randomized Subjects and Historical Controls

N/A.

9.3.3. Primary Efficacy Analyses

9.3.3.1. Analysis of the Primary Clinical Endpoint

The analysis of the primary clinical endpoint (Day 30 ± 2) will be carried out as follows:

The composite of arterial thromboembolism, venous thromboembolism, and all-cause mortality defined as follows:

1. Any arterial thromboembolic event defined by:
   a. Documented thromboembolic stroke by imaging (Head CT, Brain MRI) defined as a new focal neurologic defect lasting at least 24 hours that is not due to a readily identifiable non-vascular cause
   b. Documented peripheral arterial thromboembolism by imaging (CT scan, arteriography, arterial Doppler of extremities)
   c. Documented acute myocardial infarction defined by 2 of the 3 following conditions: 1) an appropriate clinical condition such as new EKG changes, 2) elevation of CK-MB or Troponin-T or I ≥ 2 X ULN (if CK-MB or troponin unavailable then total CK ≥ 2 X ULN), 3) new significant (≥0.04 seconds) Q waves in ≥ two contiguous leads

2. Any new venous thromboembolic event (symptomatic DVT or asymptomatic proximal DVT found by screening ultrasonography or as an incidental finding of PE on CT scan) including DVT of upper or lower extremities, PE, splanchnic vein thrombosis, cerebral vein thrombosis defined by:
   a. One or more new filing defects at compression ultrasonography, venography, CT venography, or MR venography
b. A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion scan (V/Q scan)

3. All-cause mortality
9.3.4. Secondary Analyses
The analysis of the key secondary endpoint, the composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Hospital Day 10 + 4 will be carried out in the same manner as the primary efficacy endpoint. Descriptive statistics of the other secondary endpoints, including the Sepsis-induced coagulopathy (SIC) score, ISTH DIC score, progression to Acute Respiratory Distress Syndrome (ARDS), need for intubation, re-hospitalization at Day 30 ± 2 days will also be conducted.

9.3.5. Interim Analysis
A single interim analysis is planned after the primary outcome status is observed on half (123) of the randomized patients. The interim analysis will allow early termination for evidence of efficacy if the absolute risk reduction (ARR) is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate dose group.

9.3.6. Missing Data
Every effort will be made to minimize the amount of missing data. Due to the critical and time sensitive nature of this protocol, the focus will be on three outcome variables: Day 10 +4 screening lower extremity ultrasonography and Day 30 ± 2 primary efficacy and principal safety outcomes. There should be no missing data on the most important component of the primary efficacy endpoint, all-cause mortality.
9.3.7. Sample Size and Power Calculation
Assuming a 40% relative risk reduction in the primary efficacy outcome with LMWH treatment (4) and an incidence of the primary efficacy endpoint of 42% in the usual medical care arm (2, 4, internal Northwell data), 246 patients will be needed to be enrolled (123 in each arm) to have 80% power with a two-sided significance level of 0.05. Assuming a 20% drop out rate, we will need 308 patients in total. The primary analysis will be done in the per-protocol population. The per protocol analysis set will consist of all patients who received at least 80% of planned therapy. The safety analysis will consist of all patients who received at least one dose of study medication.

9.3.8. Secondary Efficacy Analyses
The secondary outcomes described above will be analyzed using a combination of methods for continuous, ordinal, categorical and binary data.

9.4. Biomarker Analyses
N/A

9.5. Safety Analyses
Safety population: The safety population includes all randomized patients who received at least one dose of the study drug. Analysis of the safety population will be done according to the treatment received (as treated).

9.6. Data Safety Monitoring Board
An independent data safety monitoring board (DSMB) will actively monitor interim data to review the ongoing safety of patients and can make recommendations about early study closure or changes to the protocol. The DSMB members will include 2 physicians with relevant medical specialty training and 1 statistician. The DSMB will convene bi-weekly with additional meetings or conference calls scheduled as needed. The detailed operation of the DSMB is governed by a charter describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring) and requirements for reporting.

10. DATA INTEGRITY AND QUALITY ASSURANCE

10.1. Monitoring
The PI or designee will visit each site prior to enrollment and throughout the study duration to ensure safety and adherence to study protocols. The number of visits for any given site may vary based on site risk indicators. Study-related monitoring may also be done by internal and external
regulatory agencies, including the IRB and OHRP. Study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.2. Data Collection

Subjects enrolled in this study will undergo laboratory testing as part of standard-of-care. The results of these tests will be collected, as indicated. Certain tests that are not necessarily part of standard-of-care will also be collected as part of this study, as indicated. Subjects will be made aware of and will be required to consent to additional procedures during the Informed Consent process. Detailed instructions for blood/NP swab sample collections will be in the laboratory manual provided to study sites.

10.3. Data Management

A data management plan specifying all relevant aspects of data processing for the study will be maintained with the regulatory documentation for this protocol. All data coding (SAEs, baseline findings, medication, medical history, etc.) will be done using internationally recognized and accepted abbreviations. Northwell Health has designed and implemented a HIPAA compliant COVID-19 DataMart data collection tool (see Appendix G.) which will be utilized to obtain clinical data for COVID-19 patients within the health system in addition to the medical record.

10.4. Electronic Systems

Electronic systems that may be used to process data in this study will include:

- Biostatistics Randomization Management System (BRMS) –randomization
- REDCap – data collection CRF
- Statistical Analysis System (SAS) –statistical review and analysis

10.5. Study Documentation

10.5.1. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded onsite on paper Case Report Forms (CRFs), and then transferred to REDCap by trained study staff. All required CRFs must be completed for every study subject. The PI will ensure the accuracy, completeness, and timeliness of the data and will provide his electronic signature upon review. Copies of paper CRFs will be retained as part of the study record and available for inspection by regulatory authorities. The electronic systems used for data management all employ an audit trail that will reflect any changes made to study records.

10.5.2 Record Retention and Storage

All essential study documents, including ICFs, source documents, CRFs, drug accountability records, and regulatory documentation will be stored in a locked office at the Center for Health
Innovations and Outcomes Research at Northwell Health with access limited to approved study personnel only. All documents will be retained for at least 15 years following the completion or discontinuation of the study.

10.6. Operational Procedures

A ‘Meta-Site’ will be established to coordinate study personnel working remotely to perform study tasks that do not need to be completed on-site. These will include but are not limited to the following: 1) track all data, 2) coordinate meetings, 3) maintain regulatory documentation, 4) oversee study personnel and address staffing needs. A Meta-Site Principal Investigator will be identified to oversee this team.

In the event of a degradation of system-wide resources and/or significant staffing reduction due to the nature of the COVID-19 pandemic, every effort will be made to collect data as described in this protocol. A majority of data will be collected from the COVID-19 Data Mart established and maintained by the Center for Health Outcomes Research at Northwell Health. Protocol deviations will be reported as feasible. Subjects will continue to receive care while hospitalized, however will not be prioritized over non-study participants for available equipment and/or other resources.

Of note, regardless of study participation, the decision for ventilator support is based on the clinical decision making of the care team and according to Northwell Policy.

11. PUBLICATION POLICY

11.1. Publication and Public Disclosure of Clinical Trial Information
This study and results will be made publicly available on ClinicalTrials.gov. Processes for publications resulting from this study will be outlined separately.

12. ETHICS AND ADMINISTRATIVE INFORMATION

12.1. Good Clinical Practice Statement
It is the responsibility of the PI and all study personnel to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

12.2. Confidentiality
All appropriate measures will be taken to ensure that the anonymity of each subject is maintained. Subjects will be identified by an alphanumeric code only on CRFs and other related documentation. Source documentation that may not be coded will be kept confidential.

12.3. Informed Consent
It is the responsibility of the PI or other IRB-approved study personnel to obtain informed consent from each subject or a legally authorized representative (LAR) prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the potential subject in language that he/she can understand. The following procedures are based on the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic and will be applied to this study.

For patients that are able to sign for themselves:

- Healthcare worker who enters the room (can be the investigator, but does not have to be) provides the patient with a copy of the consent form
- If the consenting investigator is in the room with the patient during the consent process, the patient and the consenting investigator will sign the consent form. Witness signature will be waived. The consent process will be documented in an enrollment note as per Northwell Policy GR089.
- If direct communication with the patient is not feasible due to isolation, the investigator obtaining consent from outside of the room will arrange a three-way call or video conference with (a) the patient, (b) a witness, and (c) if desired by the patient, additional participants (e.g., next of kin)
  - The consent process will include the following steps:
    - Each attendee on the call or video conference identifies him/herself (include name and role/relationship to patient)
    - Investigator reviews the consent form with the patient and answers any questions that occur during the conversation.
    - Witness verbally confirms that patient’s questions have been answered. If the healthcare worker in the room serves as the witness, the healthcare worker must sign the consent form as witness to the consent process.
    - Investigator asks the patient to confirm that the patient is willing to participate in the trial and to sign the consent document while the witness is present or listening on the phone or video conference.
    - Patient verbally confirms that s/he would like to participate in the trial and patient signs and dates the consent form.
    - The signed consent form is collected from the patient room following infection control protocols. More specifically, pen used by patient to sign the consent form is thrown away and consent form signed by the patient is placed in a biohazard bag and then in a clean bag. Investigator will sign the consent form once the paper copy becomes available and ensure that the fully signed consent form is filed in the patient’s record.

- If it is not possible to collect the consent form due to contamination of document by infectious material, one of the following will be done:
  - The Investigator and witness will sign and date a copy the consent form and provide individual attestation using the COVID-19 Witness Attestation form & COVID-19 Investigator Attestation form that the patient agreed to participate in the study and signed the informed consent form.

OR
• The healthcare worker in the room (in her/his capacity as witness) can photograph the signature page of the consent form as signed by the patient and witness and forward to the investigator to print and place in the patient’s record. An attestation (using the COVID-19 Investigator Attestation form) by the person entering the photograph in the study record must indicate how the photograph was obtained and confirm that it is a photograph of the informed consent form signed by the patient.

When informed consent is to be obtained from a Legally Authorized Representative (LAR), who is not present due to isolation rules, and have access to email:

• The investigator will contact the LAR on the phone and request an email address to email a copy of the informed consent form.
• Consent form will be emailed to the LAR for review during consent conversation with the investigator.
• The investigator obtaining consent arranges a three way call or video conference with (a) the patient’s LAR, (b) an impartial witness, and (c) if desired by LAR, additional participants (e.g., patient’s next of kin)
  • The consent process will include the following:
    • Each attendee who is on the call or video conference identifies him/herself (include name and role/relationship to patient)
    • Investigator reviews the consent form with the LAR and answers any questions that occur during the conversation
    • Witness verbally confirms that LAR's questions have been answered
    • Investigator asks the LAR to confirm that the LAR is in agreement with patient’s participation in the trial while the witness is listening on the phone or video conference
    • LAR verbally confirms that s/he would like the patient to participate in the trial and LAR signs and dates the consent form (if feasible).
• Investigator and impartial witness will sign and date a copy of the consent form.
• Investigator will ask LAR to:
  • Sign and date the LAR’s copy of consent form and email back a scanned copy.
  OR
  • Take a photograph of the signature page of the LAR’s signed and dated consent form and forward to the investigator. The photo of the LAR’s signed and dated signature page of the consent form will be printed and placed in the patient’s record along with the paper consent form signed by the investigator and witness.
  OR
  • Send an email response to the investigator indicating agreement to allow patient’s participation in the clinical trial (if they cannot email or scan the signed consent form). The Investigator and witness will provide individual attestation that the LAR is in agreement with the patient’s participation in the study (using the COVID-19 Witness Attestation form & COVID-19 Investigator Attestation form). In addition, the investigator will send, through certified mail, a copy of the consent form to the LAR and ask for the LAR to sign and date the consent and send it back by mail for confirmation of signature.
• The enrollment note must include a description of the consent process followed and if applicable, will indicate why the original signed document was not retained (using
When informed consent is to be obtained from a Legally Authorized Representative (LAR), who is not present due to isolation rules AND does not have access to email or one does not exist, verbal consent can be obtained as follows:

- The investigator will contact the LAR on the phone and inform him/her that a three way call or video conference with (a) an impartial witness, and (b) if desired by the LAR, additional participants (e.g., patient’s next of kin) will be conducted to discuss the study.
- During the consent conversation, investigator will review the consent form with the LAR and any additional participants.
- The consent process must include the following:
  - Each attendee who is on the call or video conference identifies him/herself (include name and role/relationship to patient)
  - Investigator reviews the consent form with the LAR and answers any questions asked during the conversation
  - Impartial witness verbally confirms that LAR’s questions have been answered
  - Investigator asks the LAR to confirm that the LAR is in agreement with patient’s participation in the trial while the impartial witness is listening on the phone or video conference
  - LAR verbally confirms that s/he would like the patient to participate in the trial.
- Following the LAR’s verbal confirmation that he/she agrees to allow patient’s participation in the clinical trial, the investigator will mail a copy of the consent form to the LAR and ask for the LAR to sign and date the consent and send it back by mail for confirmation of signature.
- Investigator and impartial witness will sign and date a copy of the consent form and each will provide attestation (using the COVID-19 Witness Attestation form & COVID-19 Investigator Attestation form) that the LAR is in agreement with the patient’s participation in the study.
- The enrollment note will include a description of the consent process and if applicable, should indicate why the signed document was not retained (using the COVID-19 Enrollment Note).

Patients with Limited English Proficiency (LEP) will not be excluded from this study. Informed Consent will be obtained in this case following the procedures detailed above, using an impartial interpreter and a short form translated into the patient’s preferred language, and in accordance with Northwell Health policy GR089 for obtaining informed consent for patients with Limited English Proficiency.
12.4. Regulatory Compliance

The Northwell Health Institutional Review Board (IRB), as described in ICH guidelines for GCP, will provide regulatory oversight of this clinical study. The IRB will review and approve:

- The protocol, Informed Consent Form, and advertising materials,
- Amendments or modifications to the protocol or ICF before implementation,

In addition, the IRB will be informed of any event likely to affect the safety of patients or the conduct of the study. Records of the IRB review and approval of all study documents will be kept on file by the PI.

12.5. Protocol Deviations

Major and minor protocol deviations will be reported according to institutional policy.

12.6. New Information Affecting the Conduct of the Study
If new information affecting either the conduct of the study or the initial risk/benefit assessment becomes available, this protocol will be amended as needed and submitted for IRB review. Subjects will be informed and required to provide informed consent.

12.7. Protocol Amendments

All amendments or modifications to this protocol will be reviewed and approved by the IRB prior to implementation. In the event that a modification is required in an emergency situation, the IRB will be notified immediately.

12.8. Study Termination

The sponsor, investigator, and/or regulatory agencies have the right to terminate the study prematurely on the basis of safety, efficacy or futility.
13. REFERENCES


Northwell Health System Guidance on Cardiovascular/Thromboembolic Disease and Hospitalized Patients with COVID-19

Patients with cardiovascular disease do worse with COVID-19 and there is an increased frequency of CVD-associated SAEs associated with the coronavirus itself or with antivirals and other treatment modalities (myocarditis, acute coronary syndromes, cardiac arrhythmias, cardiogenic shock, and venous thromboembolism). There is also a worse prognosis for patients with very elevated D-dimer (>6X ULN) although mechanisms are incompletely understood: Proposed mechanisms include coagulopathy/DIC, cytokine storm, and presence of microthrombi. There may be issues of hepatic enzyme dysfunction (CYP3A4 inhibition), with the use of certain antivirals (Lopinavir/Ritonavir), which results in impaired metabolism of antithrombotics. Lastly, recent clinical data supports aggressive prophylactic-to-intermediate dose pharmacologic thromboprophylaxis with low molecular weight heparin in hospitalized COVID-19 patients with severe illness as well as extended thromboprophylaxis in high VTE risk patients (IMPROVE VTE score 4 or more, advanced age, elevated D-dimer). Key points:

- Do NOT stop antithrombotics in COVID-19 patients
- Consider changing clopidogrel/ticagrelor to prasugrel in patients on Lopinavir/Ritonavir or consider P2Y12 monitoring
- Careful consideration of apixaban/rivaroxaban in patients on Lopinavir/Ritonavir or consider dabigatran or dose adjusted warfarin
- Also consider substituting argatroban IV for UFH IV for device associated anticoagulation issues. Empiric use of treatment dose heparin (IV UFH/LMWH) or use of systemic tPA should be studied in a randomized trial setting
- For hospitalized non-ICU patients, thromboprophylaxis in patients with CrCl > 15ml/min and BMI < 30 using enoxaparin 40mg SQ QD; with BMI > 30 using enoxaparin 40mg SQ BID; in patients with CrCl < 15ml/min or RRT and BMI < 30 use UFH 5000U SQ BID or TID; in patients with CrCl 15ml/min or RRT and BMI ≥ 30 use UFH 7500U SQ BID or TID
- In ICU patients, as above but also use multimodal prophylaxis with mechanical methods (IPCs).
- Extended thromboprophylaxis with enoxaparin 40mg SQ QD or rivaroxaban 10mg PO QD for 31 – 39 days post-discharge in patients with an IMPROVE VTE score of ≥ 4 or age > 60yrs and/or elevated D-dimer (> 2X ULN).
<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets, K/µL</strong></td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>2</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>&lt;1.3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.3-1.7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.7</td>
<td>2</td>
</tr>
<tr>
<td><strong>D-Dimer, ng/mL</strong></td>
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</tr>
<tr>
<td></td>
<td>400-4000</td>
<td>2</td>
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<tr>
<td></td>
<td>&gt;4000</td>
<td>3</td>
</tr>
<tr>
<td><strong>Fibrinogen, mg/dL</strong></td>
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<tr>
<td></td>
<td>&lt;100</td>
<td>1</td>
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</table>
14.3 Appendix C

IMPROVE Bleed Score - Bleeding Risk Score Points Assigned to Each Independent Factor
*[adapted from Decousus et al Ref 16]*

<table>
<thead>
<tr>
<th>Bleeding Risk Factors</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Renal failure GFR 30–59 vs ≥60 mL/min/m²</td>
<td>1</td>
</tr>
<tr>
<td>Male vs female</td>
<td>1</td>
</tr>
<tr>
<td>Age 40–80 vs &lt;40 years</td>
<td>1.5</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>2</td>
</tr>
<tr>
<td>CV catheter</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU</td>
<td>2.5</td>
</tr>
<tr>
<td>Renal failure GFR &lt;30 vs ≥60 mL/min/m²</td>
<td>2.5</td>
</tr>
<tr>
<td>Hepatic failure (INR &gt;1.5)</td>
<td>2.5</td>
</tr>
<tr>
<td>Age ≥85 vs &lt;40 years</td>
<td>3.5</td>
</tr>
<tr>
<td>Platelets &lt;50 × 10⁹ cells/L</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding in 3 months before admission</td>
<td>4</td>
</tr>
<tr>
<td>Active gastroduodenal ulcer</td>
<td>4.5</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; CCU, critical care unit; CV, central venous; GFR, glomerular filtration rate; INR, international normalized ratio

*A score of 7 or more constitutes high bleed risk*
### Quick SOFA Score

<table>
<thead>
<tr>
<th>Assessment</th>
<th>qSOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood pressure <em>(SBP ≤ 100 mmHg)</em></td>
<td>1</td>
</tr>
<tr>
<td>High respiratory rate <em>(≥ 22 breaths/min)</em></td>
<td>1</td>
</tr>
<tr>
<td>Altered mentation <em>(GCS ≤ 14)</em></td>
<td>1</td>
</tr>
</tbody>
</table>
### The 7 Factor IMPROVE VTE RAM *(18)*

<table>
<thead>
<tr>
<th>VTE Risk Factor</th>
<th>Points for the Risk Score</th>
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<tr>
<td>Previous VTE</td>
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<tr>
<td>Thrombophilia**</td>
<td>2</td>
</tr>
<tr>
<td>Current lower limb paralysis or paresis***</td>
<td>2</td>
</tr>
<tr>
<td>Cancer****</td>
<td>2</td>
</tr>
<tr>
<td>Immobilization*****</td>
<td>1</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
</tbody>
</table>
## Study Flow Chart and Events Schedule

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening (Up to 72 hours before randomization)</th>
<th>Day 0 (Day of randomization)</th>
<th>Hospital Day 10 + 4 or discharge</th>
<th>Day 30 ± 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Medication</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Study Labs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications*</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Use of mechanical Thromboprophylaxis</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical scores**</td>
<td></td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Primary Outcome Assessment</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Secondary Outcome Assessment/SAEs</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Screening LE Doppler CUS</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*including unblinded investigational agents for COVID-19

** ISTH DIC Score, SIC score, Quick SOFA score, IMPROVE VTE Risk score, Improve Bleed Score

Systemic Anticoagulation with Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or
Intermediate Dose LMWH in High Risk COVID-19 Patients (HEP-COVID Trial)

Northwell Health HRPP: 20-0340

IND Exempt: PIND #150026

PROTOCOL VERSION: March 23rd, 2021

Proprietary and Confidential
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PROTOCOL SYNOPSIS

1. INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in Wuhan, China, on 31 December 2019. The World Health Organization (WHO) declared the outbreak a global health emergency on 30 January 2020. The infection can be transmitted by direct interpersonal contact, fomites, respiratory secretions, and direct viral shedding into the air via normal respiration. SARS-CoV-2 has been isolated from both feces and urine.

From the beginning of the month to April 15, 2020 New York State has reported over 203,377 cases of SARS-CoV-2 infection and 10,834 deaths. New York City has reported over 107,263 cases of SARS-CoV-2 infection and 10,367 deaths.

Recent data is emerging of a very high incidence of thromboembolic complications, especially venous thromboembolic (VTE) complications, in hospitalized COVID-19 patients, especially the sick hospitalized patients in Intensive Care Units (ICU) with respiratory failure. Although hospital and antithrombotic guidelines advocate for routine VTE risk assessment and use of standard thromboprophylaxis, recent reports also suggest the failure to prevent thromboembolic events in these patients using standard or routine thromboprophylaxis strategies, likely due to the prothrombotic state seen in these patients. Previous data suggests a mortality advantage in using empiric treatment dose anticoagulant therapy with heparin in patients with severe viral pneumonia.

To date, there is no data to inform the optimal dose of heparin thromboprophylaxis in the sick, hospitalized, and likely prothrombotic COVID-19 population. Multiple international antithrombotic societies have advocated high quality data to inform this critical clinical question, and to definitively answer the question of whether empiric treatment dose heparin therapy confers a net clinical benefit to reduce major thromboembolic events and associated mortality in this population.
1.1. Background

COVID-19 patients have been noted to have significantly elevated markers of hypercoagulability including d-dimer (Dd), fibrinogen levels, FVIII levels, short activated partial thromboplastin time (aPTT) and Sepsis-Induced Coagulopathy (SIC) scores with an increase in venous thromboembolic disease as well as cardiac injury, for which potential causes may include atherothrombosis, demand ischemia or microthrombosis. The mechanism underlying morbidity related to thrombosis in COVID-19 patients remains unclear [1].

There are clinical data to support the observation that hospitalized acutely ill medical patients with severe viral pneumonitis/Acute Respiratory Distress Syndrome (ARDS), such as those with influenza H1N1 infection, have an over 23-fold increased risk for venous thromboembolism (VTE) - especially pulmonary embolism (PE) - with an overall 44% incidence of VTE in ARDS associated with H1N1 pneumonia [2]. Multicenter studies from China report that key markers of inflammation and/or coagulopathy are associated with morbidity and increased mortality in COVID-19 patients. Elevated D-dimer levels (that are sometime greater than 4 or 6 times the upper limit of normal [ULN]) are strongly associated with mortality in patients with severe COVID-19 illness [3,4]. Recent data also shows that mortality among COVID-19 patients is markedly higher in patients with elevated TnT levels than in patients with normal TnT levels [5]. Recently, Cui and colleagues retrospectively evaluated a cohort of 81 patients diagnosed with severe COVID-19 pneumonia and reported a lower extremity VTE incidence of 25% (20/81) and a mortality of 40% (8/20) in the presence of VTE [6]. Danzi et al reported a case of bilateral pulmonary embolism in a 75 year old woman diagnosed with severe COVID-19, in the absence of predisposing risk factors and a negative lower extremity US [7]. Lastly Wang et al investigated the use of Tissue Plasminogen Activator (tPA) in the treatment of COVID-19 associated ARDS and reported promising, but transient, results in terms of pulmonary function improvement [8]. It appears that either the SARS-CoV2 infection itself induces a hypercoagulable state, possibly by hypofibrinolytic mechanisms, or the cytokine storm in COVID-19 patients with severe disease induces a prothrombotic state, which leads to clinical deterioration, hypoxia and hemodynamic instability secondary to thromboembolic phenomena and potentially cardiac ischemia [9]. Preliminary data from Northwell Health System, which has one of the largest populations of hospitalized COVID-19 patients in the US, reveals a positivity rate for deep vein thrombosis (DVT) of 40% of those COVID-19 patients screened by Doppler compression ultrasonography of the lower extremities (internal Northwell data).

Heparin has been shown to have anti-inflammatory and immunomodulatory properties in addition to its anticoagulation effect, which could play a beneficial role in sepsis [10]. In addition, there is in vitro evidence that the large negatively charged sulfated glycosaminoglycans of unfractionated heparin may act as an alternate ligand for the SARS-CoV2 receptor irrespective of ACE2 [4]. Whether this in vitro evidence supports the role of a protective or deleterious mechanism in COVID-19 infection is not known. However, an early report with empiric use of treatment dose unfractionated heparin (UFH) in ARDS from a different viral family, influenza H1N1, revealed that H1N1 ARDS patients under systemic anticoagulation had 33-fold fewer VTE events than those treated with prophylactic doses of UFH/low-molecular weight heparin (LMWH) thromboprophylaxis [2]. Very recent evidence suggests that therapy with prophylactic to intermediate doses of the LMWH enoxaparin (30mg to 60mg QD) in severe hospitalized COVID-19 patients with a sepsis-induced coagulopathy (SIC) score ≥ 4 or D-dimer (Dd) > 4 or even > 6 X ULN improves outcomes and prognosis [4]. All-cause mortality at 28 days was reduced from 64.2% to 40.0% in those patients with a SIC score ≥ 4 (p=0.029), and from 52.4% to 32.8% in those patients with an elevated Dd >
6 x ULN (P=0.017) (4). Notably, Klok and colleagues investigated 184 ICU patients infected with COVID-19 and reported a 13% mortality rate, a relatively high incidence of CTPA- or ultrasonography-confirmed VTE rate (27%), and arterial thrombotic events (3.7%) despite the use of standard dose thromboprophylaxis [11]. Postulated mechanisms for the improved prognosis with
the use of treatment doses of LMWH in the sick COVID-19 population include the decrease in the risk of microthrombi, especially in the pulmonary vasculature, which can lead to hypoxemia, pulmonary vasoconstriction and right ventricular dysfunction as well as the decrease in the risk of progression to disseminated intravascular coagulopathy as a contributor to the high mortality seen in these patients [12].

### 1.1.1. Pharmaceutical and Therapeutic Background

The optimal dose of heparin (either LMWH or UFH) in hospitalized COVID-19 patients is unknown, as patients on conventional prophylactic dose heparin (UFH or LMWH) as supported by international guidance statements on hospitalized COVID-19 patients appear to remain at risk for thromboembolic events [13]. There is data to support improved efficacy with treatment doses of twice daily enoxaparin versus once-daily weight-adjusted enoxaparin for the management of VTE, especially with large thrombus burden [14]. There is also long-standing data to support that treatment-dose heparin can reduce major cardiovascular events [15]. Our current standard of care in our 24 hospital Northwell Health System, which has a very large hospitalized COVID-19 patient population, is to use Lovenox 40mg SQ QD for patients with a BMI < 30 and Creatinine Clearance (CrCl) > 15ml/min, Lovenox 40mg SQ BID for patients with a BMI > 30 and CrCl > 15ml/min, and UFH 5000U SQ BID or TID in patients with a CrCl < 15ml/min and BMI < 30 and UFH 7500U SQ BID or TID with a CrCl < 15ml/min and BMI > 30. (Appendix A). Large healthcare institutions in the US and elsewhere have protocols for in-patient thromboprophylaxis ranging from prophylactic-to-intermediate dose UFH or LMWH for the management of patients with COVID-19 associated coagulopathy [16]). The aim of this study is to test the hypothesis that prophylaxis of severe COVID-19 patients with treatment dose LMWH leads to better thromboembolic-free outcomes and associated complications during hospitalization than prophylaxis with institutional standard of care with prophylactic to intermediate-doses of UFH or LMWH.
2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

Our hypothesis is that sick hospitalized COVID-19 patients receiving therapeutic doses of heparin (LMWH) during hospitalization will show a reduction of the primary and secondary endpoints that are associated with a prothrombotic state within 30 days of their hospital admission.

2.1.1. Primary Objective

The overall objective of the study is to evaluate the clinical efficacy of therapeutic low molecular weight heparin (LMWH) versus prophylactic/intermediate doses of UFH or LMWH as per local institutional protocols in reducing the composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Day 30 ± 2 days.

2.1.2. Secondary Objectives

To evaluate the safety of such an approach by assessing the risk of major bleeding defined using the International Society of Thrombosis and Haemostasis (ISTH) criteria at Day 30 ± 2 days.
2.2. **Hypothesis**

Patients receiving therapeutic doses of heparin (LMWH) patients will show a reduction of the primary and secondary endpoints that are associated with a prothrombotic state within 30 ± 2 days of their hospital admission.

2.3. **Study Endpoints**

2.3.1. **Primary Efficacy Endpoints**

Primary Clinical Endpoint: The composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Day 30 ± 2 days.

1. **Any arterial thromboembolic event defined by:**
   a. Documented thromboembolic stroke by imaging (Head CT, Brain MRI) defined as a new focal neurologic defect lasting at least 24 hours that is not due to a readily identifiable non-vascular cause
   b. Documented peripheral arterial thromboembolism by imaging (CT scan, arteriography, arterial Doppler of extremities)
   c. Documented acute myocardial infarction defined by 2 of the 3 following conditions: 1) an appropriate clinical condition such as new EKG changes, 2) elevation of CK-MB or Troponin-T or I ≥ 2 X ULN (if CK-MB or troponin unavailable then total CK ≥ 2 X ULN), 3) new significant (≥0.04 seconds) Q waves in ≥ two contiguous leads

2. **Any new venous thromboembolic event (symptomatic DVT or asymptomatic proximal DVT found by screening ultrasonography or as an incidental finding of PE on CT scan) including DVT of upper or lower extremities, PE, splanchnic vein thrombosis, cerebral vein thrombosis defined by:**
   a. One or more new filing defects with venography, CT venography, or MR venography
   b. A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion scan (V/Q scan)
   c. A non-compressible venous segment on compression ultrasonography, or in patients with a history of previous DVT, either a new non-compressible segment or a substantial increase (4mm or more) in the diameter of the vein during full compression in a previously abnormal segment on ultrasonography
   d. In the absence of an imaging test in a hemodynamically unstable patient, evidence of right ventricular dysfunction by transthoracic or trans esophageal echocardiogram (ESC Criteria)

3. **All-cause mortality**
Principal Safety-endpoint: Major bleeding using ISTH criteria at 30 ± 2 days.

1. Documented major bleeding using ISTH criteria defined by:
   a. A decrease in hemoglobin of 2g/dl or more within 24 hours
   b. A transfusion of 2 or more units of packed red blood cells
   c. Critical site bleeding (including intracranial, intraocular, intra-articular, retroperitoneal, intramuscular with component syndrome, pericardial)
   d. Bleeding that is fatal
   e. Bleeding that necessitates surgical intervention

2.3.2. Secondary Efficacy Endpoint
The composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal and distal DVT of the lower extremity, non-fatal pulmonary embolism (PE), and all-cause mortality at Hospital Day 10 + 4

Progression to Acute Respiratory Distress Syndrome (ARDS), new-onset atrial fibrillation (AF), acute kidney injury (AKI), non-fatal cardiac arrest, need for intubation, need for Extracorporeal Membrane Oxygenation (ECMO), re-hospitalization at Day 30 ± 2 days.
3. STUDY DESIGN

3.1. Overall Design

Prospective Open-label Randomized Trial using an Active Control Group, with patients stratified by ICU stay or Non-ICU stay
3.1.1. Study Duration
The study is expected to last for up to twelve months.

3.1.2. Duration of Study Participation
An individual subject will complete the study in about 30 ± 2 days, from screening at Day -1 or 1 to follow-up visit on Day 30 ±2 days. If a participant is unable to return to the site for Day 30±2 assessment, safety will be assessed via Telemedicine or telephone contact.

4. STUDY POPULATION

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

4.1.1.1. Inclusion Criteria for Study Subjects
1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
4. Subject consents to randomization within 72 hours of hospital admission or transfer from another facility within 72 hours of index presentation.
5. Subjects with a positive COVID-19 diagnosis by nasal swab or serologic testing
6. Hospitalized with a requirement for supplemental oxygen
7. Have:
   • Either a D- Dimer > 4.0 X ULN OR
   • Sepsis-induced coagulopathy (SIC) score of ≥4 (Appendix B)
4.1.2. Exclusion Criteria

1. Indications for therapeutic anticoagulation

2. Absolute contraindication to anticoagulation including:
   a. active bleeding,
   b. recent (within 1 month) history of bleed,
   c. dual (but not single) antiplatelet therapy,
   d. active gastrointestinal and intracranial cancer,
   e. a history of bronchiectasis or pulmonary cavitation,
   f. Hepatic failure with a baseline INR > 1.5,
   g. CrCl < 15ml/min,
   h. a platelet count < 25,000,
   i. a history of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies.
   j. contraindications to enoxaparin including a hypersensitivity to enoxaparin sodium, hypersensitivity to heparin or pork products, hypersensitivity to benzyl alcohol
   k. pregnant females
   l. inability to give or designate to give informed consent
   m. participation in another blinded trial of investigational drug therapy for COVID-19

(Applies to both Study Subjects and Randomized Subjects)

4.1.2.1. Rationale for Selected Exclusion Criteria
LMWH has a well-established risk of clinically important bleeding, including major and fatal bleeding, with therapeutic doses of drug increasing this risk. The clinical exclusionary criteria as established by previous randomized trials of anticoagulant therapy in patients with thrombotic disorders and as used by the Hep-COVID trial represent well-established high clinical bleed risk factors. Pregnant women will be excluded due to uncertain characterization of the risk of VTE when hospitalized with COVID-19 with unlikely net clinical benefit from an aggressive thromboprophylactic strategy.
5. STUDY TREATMENTS

5.1. Assigning Randomized Subjects to Treatments

5.1.1. Stratification

Prior to randomization, subjects will be stratified according to whether they are in a designated ICU unit or not.

5.1.2. Randomization

This study is a randomized, controlled trial using open-label active controls to evaluate the efficacy and safety of treatment dose LMWH versus prophylactic/intermediate dose LMWH in sick hospitalized adult patients diagnosed with COVID-19 during their hospitalization. The study is a multi-site trial that will be conducted both in hospitals within the Northwell Health system in New York as well as other health systems in United States. The study will compare the following two active treatment arms that patients received during their hospitalization:

Arm 0: Treatment Arm

- Enoxaparin 1mg/kg SQ BID for CrCl ≥ 30ml/min at randomization
- Enoxaparin 0.5mg/kg SQ BID for CrCl ≥ 15ml/min and < 30ml/min at randomization

Arm 1: Prophylactic/Intermediate Dose Arm

Local institutional standard-of-care for prophylactic-dose or intermediate-dose UFH or LMWH. Regimens allowed are:

- UFH up to 22,500 IU daily in BID or TID doses (i.e. UFH 5000 IU SQ BID/TID or 7500 IU BID/TID)
- Enoxaparin 30mg and 40mg SQ QD or BID (the use of weight-based enoxaparin i.e. 0.5mg/kg SQ BID for this arm is acceptable but strongly discouraged)
- Dalteparin 2500IU or 5000 IU QD

Randomization into Arms 0 and 1 will be carried out using a balanced 1:1 design

The Biostatistics Unit will develop and implement the randomization procedure using the Biostatistics Randomization Management System (BRMS). The Biostatistics Randomization Management System (BRMS) is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using their personal computer. The BRMS allows for multi-center, stratified, and single/double blinded RCTs, using permuted blocks. Randomization notifications (respectful of blinding status) are automatically sent
to the PI and other authorized personnel. Due to the pragmatic nature of this study “open-label multicenter randomized active control trial with pseudo-blinding” mechanisms at the time of randomization the study subject and corresponding Site PIs will be blinded (unaware of specific treatment arm the patient is assigned to i.e. Arm 0 or Arm 1). The study pharmacists as well as data extractors and designated randomization personnel (i.e. research coordinators and/or research nurses performing the randomization process) will be un-blinded (aware of specific
treatment arm the patient is assigned to i.e. Arm 0 or Arm 1). BRMS also includes a feature that allows for medically indicated breaking of the blind, with requirement for justification without violating the protocol. BRMS includes an audit trail of all transactions (Appendix 1)

A site research coordinator or designee will notify site pharmacist(s) of a newly enrolled subject, the status of informed consent, and other pertinent information such as patient name, date of birth, subject number, and location. Upon randomization by the investigator or designee, the Biostatistics Randomization Management System (BRMS) will automatically notify research pharmacist of the assigned treatment arm. The pharmacist will determine the drug dose for Arm 0, based on section 5.1.2, and for Arm 1, based on local standard of care including guidance found in (Appendix A). The pharmacist will enter the drug order using an order entry system on behalf of the investigator.
5.2. Study Drugs (commercial supply)

- Enoxaparin injection in commercially available pre-filled syringes and vials
- Unfractionated heparin injection, in commercially available vials

5.2.1. Description

Enoxaparin injection and unfractionated heparin are anticoagulant medications approved for use to prevent thromboembolic complications. Both medications as per protocol are approved for use in hospitalized patients.

5.2.2. Preparation

Enoxaparin injection is available as a 300 mG/3mL vial as well as pre-filled syringes in 40mg, 60mg, 80mg, 100mg, 120mg, or 150mg. Unfractionated heparin injection is available in multi-dose vials. The pharmacists will calculate and prepare doses based on local standard of care including guidance found in Appendix A and dispense the doses in a blinded manner, if possible.

15.2.3 Administration

Enoxaparin injection will be administered at a dose of 1mg/kg SQ BID for CrCl ≥ 30ml/min (0.5mg/kg SQ BID for CrCl ≥ 15ml/min and < 30ml/min) or as per local institutional protocols for prophylactic or intermediate-dose use. UFH will be administered as per local institutional protocols for prophylactic or intermediate dose use. Patients will have study drug administered for the duration of their hospitalization.

CrCl will be calculated using Cockcroft-Gault equation.

If height is not obtainable to calculate CrCl, then the use of estimated GFR is acceptable to calculate LMWH and UFH doses, although discouraged.

15.2.4 Storage

Enoxaparin and unfractionated heparin injections can be stored at room temperature.
15.2.5 Pregnancy
Pregnant females are excluded from the present study.

15.2.6 Contraception
Women of childbearing age must agree to use contraception for the duration of study treatment prior to providing consent.

15.2.7 Adverse Reactions
Heparin (UFH or LMWH) including enoxaparin is usually well tolerated; most adverse reactions have been mild and transient. Some common adverse reactions include: anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, nausea, fever, edema, peripheral edema, dyspnea, bleeding gums, nosebleeds, prolonged bleeding from cuts, confusion and injection site pain. There is an unlikely risk of serious allergic reactions with Enoxaparin. In some cases, there have been reports of spinal/epidural hematomas in patients receiving neuraxial anesthesia or undergoing spinal puncture.

5.3. Drug Dispensation Documentation
Pharmacy will dispense the dose(s) as per local pharmacy site procedure and maintain a subject-specific dispensing record (Appendix L). All records will be made available for inspection by regulatory agencies, and kept on file onsite as per local institutional policy (Appendix K).

5.4. Guidelines for Delay, Reduction and/or Discontinuation of Study Medications
Dose modification for an individual subject is not permitted unless the following ensues. Modification of study medication is allowed in Arm 0 (treatment arm with enoxaparin) if the CrCl falls < 15ml/min. In that instance conversion to dose adjusted IV UFH is acceptable during the time that the CrCl remains < 15ml/min. If the patient cannot be placed on UFH IV (difficult to obtain frequent aPTT draws, etc), an acceptable alternative is the use of UFH SQ using the fixed-dose weight-adjusted FIDO regimen, 333U/kg SQ, followed by 250U/kg Q12 hours, without the need to obtain aPTT monitoring. The investigator is then encouraged to convert back to treatment dose enoxaparin as per protocol once the CrCl ≥ 15ml/min. Modification is allowed in Arm 1 (prophylactic group) if the CrCl falls < 15ml/min to use UFH up to 22,500 U daily (i.e. UFH 5000u SQ BID or TID or 7500IU SQ BID or TID). The investigator is then encouraged to convert back to prophylactic/intermediate dose enoxaparin as per protocol once the CrCl ≥ 15ml/min if a subject requires permanent discontinuation of study medication they will be withdrawn from the study and standard of care treatment will be initiated.

5.5. Prior and Concomitant Medications
Concomitant use of hepatotoxic medications, immunosuppressive therapy and/or investigational study drugs for the treatment of COVID-19 with the exception of blinded investigational therapies
for COVID-19 are permitted as per usual standard of care. Any other treatment administered from the first dose of study drug to the final study assessment will be considered concomitant medication and recorded per subject.
5.6. Method of Assessing Treatment Compliance

Study drugs will be administered per protocol while subjects are hospitalized. Medication records will be made available for inspection by the sponsor and/or regulatory agencies, and kept on file onsite as per local institutional policy.

5.7. Subject Withdrawal/Discontinuation

A subject has the right to withdraw from the study at any time. The investigator and/or sponsor have the right to withdraw a subject from the study if it is no longer in the best interest of the subject to continue, or if the subject’s continuation in the study places the scientific outcome of the study at risk.

5.7.1. Subject Replacement

Due to the large target enrollment and short treatment duration of this study, withdrawn subjects will not be replaced.
6 STUDY PROCEDURES (applied to concurrent randomized subjects only)

6.1 Screening

Upon admission, the research coordinator will be notified about potentially eligible patients who require screening. The lab parameters required to determine eligibility are part of standard of care and will be available to the research coordinator shortly after admission. There will be an up to a 72 hour window from admission or transfer from another facility within 72 hours of index presentation by which to randomize patients into the trial.

6.2 Enrollment

Upon meeting the inclusion/exclusion criteria including consent, the research coordinator will officially enroll the subject and implement the randomization procedure.

6.3 Treatment Period

Treatment with study medication enoxaparin will be for the duration of hospitalization.

In the post-hospital discharge period, patients will receive post-hospitalization thromboprophylaxis as per local institutional protocols. The use of extended thromboprophylaxis for approximately 30 days’ post-hospital discharge is strongly encouraged but not mandatory. Northwell Health institutional protocols mandate thromboprophylaxis with either enoxaparin 40mg SQ QD or rivaroxaban 10mg PO QD for up to 39 days at the discretion of the investigator (Appendix A). However, other antithrombotic therapy, including low dose apixaban 2.5mg PO BID and low dose aspirin, is permitted, although discouraged.

No additional research procedures are indicated.

6.4 Follow-up

Subjects will be followed at Hospital Day 10 + 4, and for Day 30 ± 2.

7 EFFICACY ASSESSMENTS

At Hospital Day 10 + 4 or sooner at the time of hospital discharge, there will be a lower extremity Duplex screening compression ultrasonography using standardized screening methods. Confirmatory lower extremity ultrasound of symptomatic DVT or asymptomatic screening of lower extremity DVT is recommended using full duplex Doppler compression ultrasonography of the entire extremity venous system. Where resource constraints or local institutional policies preclude use of full ultrasound, point-of-care ultrasound using two-region compression can be substituted and has shown reasonable accuracy (Appendix C). There will also be an assessment of the primary efficacy, principal safety, and secondary outcomes

At Day 30 ± 2, there will be an assessment of the primary efficacy, principal safety, and secondary
outcomes via a face-to-face or telephonic visit.
8  SAFETY EVALUATION AND REPORTING

8.1  Assessment of Safety Endpoints
Subject safety will be assessed continuously while hospitalized as per standard of care for hospitalized patients. Upon discharge, subject safety will be assessed at a follow up visit on Day 30 ±2. Subjects unable to return will be assessed via Telemedicine or by telephone.

8.2  Adverse Events and Serious Adverse Events

8.2.1 Definition of Adverse Event (AE)
Adverse event (AE) is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.2.2. Definition of Serious Adverse Event (SAE)
An adverse event (AE) or suspected adverse reaction 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. 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
8.2.3. Classification of Adverse Event

8.2.3.1. Severity of Event
The following guidelines will be used to describe severity of Adverse Events (AE):

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.2.3.2. Relationship to Study Intervention
All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
• **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).

• **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

### 8.2.3.3. Expectedness

The DSMB will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### 8.2.4. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE if it meets reporting criteria.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded. Events will be followed for outcome information until resolution or stabilization.

### 8.2.5. Adverse Event Reporting

Adverse events (AEs) will be reported immediately to the PI and the Co-Investigators. It will also be reported to all members of the research team, and to the local IRB if it meets the local IRB’s reporting requirements. The PI and Co-Investigators will be notified of Adverse events (AEs)
occurring at high frequency during study duration.
8.2.6. Serious Adverse Event Reporting

The study clinician will immediately report any serious adverse event (SAE), whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event will be recorded.

The Principal Investigator (PI) will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after initial receipt of the information.
8.2.7. Reporting Events to Participants
Participants will not be informed of AEs and SAEs unless the AE or SAE happened to them.

8.2.8. Events of Special Interest
SAEs of special interest will include hypersensitivity reactions, including Steven Johnson’s syndrome, evidence of hepatic toxicity with transaminase elevations greater than 6 times the upper limit of normal, the onset of heparin-induced thrombocytopenia, and bone marrow toxicity.

8.2.9. Reporting of Pregnancy
N/A

8.3. Unanticipated Problems

8.3.1. Definition of Unanticipated Problems (UP)
The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

• Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
• Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
• Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2. Unanticipated Problem Reporting
The investigator or study team member who becomes aware will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Principal Investigator (PI). The UP report will include the following information:
• Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
• A detailed description of the event, incident, experience, or outcome;
• An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
• A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

• UPs that are serious adverse events (SAEs) will be reported within 5 business days of the investigator becoming aware of the event.
• Any other UP will be reported within 5 business days of the investigator becoming aware of the problem.

8.4. Other Safety

8.4.1. Clinical Laboratory Evaluations
Laboratory values will be obtained by venipuncture and evaluated on the day of randomization:

1. PT/INR (standard of care)
2. Platelet count (standard of care)
3. Hemoglobin/hematocrit (standard of care)
4. Serum creatinine (standard of care)
5. D-dimer (allowed within 72 hours prior to randomization) (standard of care)
6. C-reactive protein (CRP) (allowed within 72 hours prior to randomization) (standard of care)
7. Fibrinogen (allowed within 72 hours prior to randomization) (standard of care)
8. Troponin (allowed within 72 hours prior to randomization) (standard of care)
9. Protein C antigen/activity and Protein S Antigen/activity (allowed within 72 hours prior to randomization) (research purposes)
10. Antithrombin activity (allowed within 72 hours prior to randomization) (research purposes)
11. Quick SOFA score (Appendix D) (allowed within 72 hours prior to randomization)
12. ISTH SIC score (Appendix B) (allowed within 72 hours prior to randomization)
13. IMPROVE VTE score (Appendix E) (allowed within 72 hours prior to randomization)
14. Medical History (including comorbid conditions such as congestive heart failure, diabetes mellitus, a history of cardiovascular disease including venous thromboembolism and peripheral vascular disease, history of atrial fibrillation, known thrombophilia, history of hypertension, a history of dyslipidemia, a history of coronary artery disease or congestive heart failure, a history of renal or lung disease, a history of liver disease, a history of thyroid disease, a history of cancer, a history of autoimmune disease, a history of bleeding diathesis, recent surgery or trauma, tobacco use)
15. Relevant medications (all antiplatelet agents such as aspirin, clopidogrel, ticagrelor, prasugrel, vorapaxar, cangrelor; thrombolytic agents such as tPA; steroids; use of chloroquine or hydroxychloroquine; hormonal therapy; use of famotidine, immunosuppressant or immunomodulatory agents, antivirals, non-steroidal anti-inflammatory agents)

16. Use of IVC filter
17. Mechanical thromboprophylaxis (intermittent pneumatic compression devices, graduated compression stockings)

After randomization, the following data will be captured and collected as per trial protocol on Hospital Day 10 + 4 or at the time of discharge, whichever comes first:

1. PT/INR (standard of care)
2. Platelet count (standard of care)
3. Hemoglobin/hematocrit (standard of care)
4. Serum creatinine (standard of care)
5. D-dimer (standard of care)
6. C-reactive protein (CRP) (research purposes)
7. Fibrinogen (research purposes)
8. Troponin (research purposes)
9. Quick SOFA score (Appendix D)
10. ISTH SIC score (Appendix B)
11. IMPROVE VTE score (Appendix E)
12. Relevant medications (all antiplatelet agents such as aspirin, clopidogrel, ticagrelor, prasugrel, vorapaxar, cangrelor; thrombolytic agents such as tPA; steroids; use of chloroquine or hydroxychloroquine; hormonal therapy; use of famotidine, immunosuppressant or immunomodulatory agents, antivirals, non-steroidal anti-inflammatory agents).
13. Use of IVC filter
14. Mechanical thromboprophylaxis (intermittent pneumatic compression devices, graduated compression stockings)

8.4.2. Vital Signs
Vital signs will be collected daily as per the standard of care for hospitalized patients.

8.4.3. Physical Examination
Changes in clinical severity will be assessed via physical examinations.

8.4.4. Other Examinations
Lower extremity Duplex screening compression ultrasonography will be done at Hospital Day 10+4 or sooner at the time of hospital discharge using standardized screening methods.

There will be a 30 ± 2 day face to face or telephonic visit to assess study outcomes including the primary efficacy and principal safety outcomes or adverse events

Patients will be on standard medical therapy for COVID 19 as per one’s institutional guidelines and policies. Patients participating in another clinical trial of blinded investigational drug therapies for COVID-19 will be excluded. The management of adverse events such as heparin-induced thrombocytopenia, an arterial or venous thromboembolic event, or major or critical site bleeding event will be as per usual medical care. There is guidance to suggest that a dose increase of LMWH by 25% is acceptable to treat refractory thrombosis despite adequate weight adjusted treatment doses of LMWH [17,18]. For patients that need temporary interruption of study medication for an
invasive procedure or surgery, investigators will follow local established guidelines for both doses of enoxaparin. If a patient develops severe renal failure with a CrCl $< 15\text{ml/min}$ during the course of their hospitalization, their study medication will be switched to intravenous or subcutaneous unfractionated heparin as per usual care using one’s institutional guidelines (Appendix A).
For patients with rising troponins and electrocardiographic changes that reflect standard definitions of NSTEMI recommendations will be made to start aspirin regardless of heparin dose.

Other examinations may include nasopharyngeal swabs to analyze virologic clearance per standard of care for COVID-19 patients.

Additional SOC examinations performed during the inpatient treatment period will be documented in the subject file and reviewed to assess safety.

9 STATISTICAL METHODS

9.1 General Statistical Considerations

The primary clinical objective is to compare the incidence of the primary safety and efficacy outcomes, and secondary outcomes at Day 30 ± 2 days between patients receiving full dose LMWH treatment and patients receiving prophylactic/intermediate dose UFH or LMWH. A key secondary endpoint to compare the incidence of the primary safety and efficacy outcomes, and secondary outcomes at Hospital Day 10 ± 4.

9.2 Analysis Sets

Assuming a 40% relative risk reduction in the primary efficacy outcome with LMWH treatment (4) and an incidence of the primary efficacy endpoint of 42% in the usual medical care arm (2, 4, internal Northwell data), 246 patients will be needed to be enrolled (123 in each arm) to have 80% power with a two-sided significance level of 0.05. Assuming a 20% drop out rate, we will need 308 patients in total. The Intent-To-Treat (ITT) Population will consist of all subjects that were randomized. The Safety (SAF) Population, consisting of all randomized patients who received at least one dose of the study drug. This is also known as the modified intent to treat population or mITT. Reporting of the SAF population will be done according to the majority treatment received (as treated), whereas analysis of the mITT population will be analyzed according to randomization assignment. The Per Protocol (PP) Population will consist of all patients who received at least 80% of planned therapy and did not have any major protocol deviations. Planned therapy will be calculated as the duration in days that the subject received study treatment according to randomization arm divided by the duration of hospitalization after randomization, in days. Major protocol deviations can be assessed from the database and will include those patients that did not meet inclusion criteria or met exclusion criteria, permanently discontinued assigned study medication after randomization not due to an outcome event, and did not undergo the Day 10+4 lower extremity (LE) Screening Doppler compression ultrasonography (CUS).

The primary analysis will be done in the per-protocol population. The primary analysis will be conducted in the mITT population as well. There will be a single interim analysis as described below. Under the design assumptions with 246 patients, therapeutic dose treatment with LMWH treatment will be deemed to be superior to prophylactic/intermediate dose UFH or LMWH treatment (i.e., 2-sided p < 0.05) if upon trial completion the absolute risk reduction with therapeutic LMWH group is -0.117 (11.7%) lower than in the prophylactic/intermediate dose group. A single interim analysis is planned after the primary outcome status is observed on half (123) of the randomized patients. The interim analysis will allow early termination for evidence of efficacy if the absolute risk reduction (ARR) is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate
dose group. **Table 1** shows the statistical inference that would be reported if the trial stops at the critical value (15 fewer events) at both the interim and final analyses. **Table 2** shows the statistical operating characteristics of the design.
Table 1: Statistical inference upon trial completion.

<table>
<thead>
<tr>
<th></th>
<th>Efficacy Decision</th>
<th>Futility Decision</th>
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<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>CIlo</td>
</tr>
<tr>
<td>Interim Analysis</td>
<td>-0.234</td>
<td>(-0.338, -0.068)</td>
</tr>
<tr>
<td>Final Analysis</td>
<td>-0.117</td>
<td>(-0.234, 0.000)</td>
</tr>
</tbody>
</table>

For example, the trial will stop for efficacy at the interim analysis if the ARR is smaller than -0.234 (23.4% reduction in risk of the primary efficacy event. The trial will stop for futility if the risk of event is larger with therapeutic dosing than with prophylactic dosing. The study will continue to the final analysis if the observed ARR is between -0.234 and 0.000. At the final analysis superiority is decided (1-sided p<0.025) if the observed ARR is smaller than -0.0117. The confidence intervals and p-values show the result that would be reported (e.g., the hypotheses that would be ruled out) if the observed ARR was equal to the decision boundary. For example, if the observed ARR equals -0.234 at the interim analysis, then the 95% confidence rules out reductions smaller than 33.8% or larger than 6.8% with 1-sided p=0.0027.
Table 2: Statistical properties of the interim monitoring design.

<table>
<thead>
<tr>
<th>True treatment effect</th>
<th>Statistical properties of the design</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Power</td>
</tr>
<tr>
<td>P1</td>
<td>ARR</td>
</tr>
<tr>
<td>0.252</td>
<td>-0.168</td>
</tr>
<tr>
<td>0.210</td>
<td>-0.210</td>
</tr>
<tr>
<td>0.168</td>
<td>-0.252</td>
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</table>

The statistical properties of the interim analysis design include the power the average sample size of trials that are monitored using this design and the probability of stopping at the interim analysis. These properties are a function of the true treatment effect; specifically, ARR = -0.168, ARR = -0.210, and ARR = -0.252 denotes a relative risk of 60%, 50%, and 40% of therapeutic dose relative to prophylactic dose (risk = 0.42); e.g. P1= 0.252 = 0.42*0.6 so ARR = 0.252 - 0.420 = -0.168

9.3 Efficacy Analyses

9.3.1 Summaries of Baseline Demographic and Clinical Data
All baseline demographics and clinical data will be summarized by treatment arm using frequencies, rates, means, medians, standard deviations and quartiles appropriate to the dataset. There will be no inferential comparison of treatment arms with respect to baseline and demographic clinical data; such comparisons will be descriptive only. Unless otherwise specified, all results will be considered significant if p<0.05.

9.3.2 Comparability of Randomized Subjects and Historical Controls
N/A.

9.3.3 Primary Efficacy Analyses

9.3.3.1 Analysis of the Primary Clinical Endpoint

The analysis of the primary clinical endpoint (Day 30 ± 2) will be carried out as follows:

The composite of arterial thromboembolism, venous thromboembolism, and all-cause mortality defined as follows:

1. Any arterial thromboembolic event defined by:
   a. Documented thromboembolic stroke by imaging (Head CT, Brain MRI) defined as a new focal neurologic defect lasting at least 24 hours that is not due to a readily identifiable non-vascular cause
   b. Documented peripheral arterial thromboembolism by imaging (CT scan, arteriography, arterial Doppler of extremities)
   c. Documented acute myocardial infarction defined by 2 of the 3 following conditions: 1) an appropriate clinical condition such as new EKG changes, 2) elevation of CK-MB or Troponin-T or I
≥ 2 X ULN (if CK-MB or troponin unavailable then total CK ≥ 2 X ULN), 3) new significant (≥ 0.04 seconds) Q waves in ≥ two contiguous leads
2. Any new venous thromboembolic event (symptomatic DVT or asymptomatic proximal DVT found by screening ultrasonography or as an incidental finding of PE on CT scan) including DVT of upper or lower extremities, PE, splanchnic vein thrombosis, cerebral vein thrombosis defined by:
   a. One or more new filing defects at compression ultrasonography, venography, CT venography, or MR venography
   b. A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion scan (V/Q scan)
   c. A non-compressible venous segment on compression ultrasonography, or in patients with a history of previous DVT, either a new non-compressible segment or a substantial increase (4mm or more) in the diameter of the vein during full compression in a previously abnormal segment on ultrasonography
   d. In the absence of an imaging test in a hemodynamically unstable patient, evidence of right ventricular dysfunction by transthoracic or trans esophageal echocardiogram (ESC Criteria)

3. All-cause mortality
9.3.4 Secondary Analyses

The analysis of the key secondary endpoint, the composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis (DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal pulmonary embolism (PE)), and all-cause mortality at Hospital Day 10 + 4 will be carried out in the same manner as the primary efficacy endpoint. Descriptive statistics of the other secondary endpoints, including the Sepsis-induced coagulopathy (SIC) score, progression to Acute Respiratory Distress Syndrome (ARDS), new-onset atrial fibrillation (AF), acute kidney injury (AKI), non-fatal cardiac arrest, need for intubation, need for Extracorporeal Membrane Oxygenation (ECMO), re-hospitalization at Day 30 ± 2 days will also be conducted.

Multiple Thrombotic Events -

Two secondary analyses will be carried out to address the issue of multiple thrombotic events. Specifically, these analyses will address the following question and hypothesis:

**Question:** Does intensity of antithrombotic therapy change the risk for multiple thrombotic events?

Multiple thrombotic events are associated with greater morbidity and mortality and are an indication of a worse prognosis after the 30-day outcome period in this trial.

**Hypothesis:** When compared to prophylactic therapy, therapeutic antithrombotic therapy will reduce the risk of multiple thrombotic events.

The hypothesis will be evaluated in two analyses: the first (analysis A) will compare the number of thrombotic events in all randomized subjects and the second (analysis B) will compare the number of additional thrombotic events among patients who experienced at least one event. Both analyses will evaluate the ratio of rate of thrombotic events in the two randomized groups using a Poisson probability model. (The Poisson modeling will also include consideration of a zero-inflated Poisson regression model or a negative binomial over-dispersion model. Goodness-of-fit tests available in SAS will be used to explore the use of these two alternative models.)

**Analysis A:** Comparison of the incidence rate for thrombotic events in all randomized subjects.

**Analysis set:** All randomized subjects with separate analyses for the mITT and per protocol sets

**Analysis approach:** Poisson regression with the following parameterization:

**Event definition:** All thrombotic events including thrombosis-related death using protocol definitions.

**Exposure time:** Time from randomization until the earliest of the 30-day outcome assessment, withdrawal of consent, or death. Exposure time will be included as an "offset" in the Poisson model.

**Explanatory variable:** Treatment group assignment.

**Interpretation:** The rate ratio is an expression of the relative risk of one or more thrombotic event with therapeutic antithrombotic therapy relative to prophylactic therapy. The analysis will report the estimated rate ratio, the 95% confidence interval, and the p-value for testing whether the ratio differs from 1.

**Analysis B:** Comparison of the incidence rate for subsequent thrombotic events following the first such event.

**Analysis set:** All randomized subjects who experienced a first thrombotic event. Subjects who died of their first thrombotic event or who died of other causes without a thrombotic event will be excluded. Subjects who did not experience a thrombotic event will also be excluded. Separate
analyses will be conducted for the mITT and per protocol sets.

**Analysis approach:** Poisson regression with the following parameterization:

**Event definition:** All thrombotic events subsequent to the first event including thrombosis-related death following a first event.

**Exposure time:** Time from the first thrombotic event to the earliest of the 30-day outcome assessment, withdrawal of consent, or death. Exposure time will be included as an "offset" in the Poisson model.

**Explanatory variable:** Treatment group assignment.

**Interpretation:** The rate ratio is an expression of the relative risk of subsequent thrombotic events with therapeutic antithrombotic therapy relative to prophylactic therapy. The analysis will report the estimated rate ratio, the 95% confidence interval, and the p-value for testing whether the ratio differs from 1.

### 9.3.5 Interim Analysis

A single interim analysis is planned after the primary outcome status is observed on half (123) of the randomized patients. The interim analysis will allow early termination for evidence of efficacy if the absolute risk reduction (ARR) is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate dose group.

### 9.3.6 Missing Data

Every effort will be made to minimize the amount of missing data. Due to the critical and time sensitive nature of this protocol, the focus will be on three outcome variables: Day 10 +4 screening lower extremity ultrasonography and Day 30 ± 2 primary efficacy and principal safety outcomes. There should be no missing data on the most important component of the primary efficacy endpoint, all-cause mortality
9.3.7 Sample Size and Power Calculation
Assuming a 40% relative risk reduction in the primary efficacy outcome with LMWH treatment (4) and an incidence of the primary efficacy endpoint of 42% in the usual medical care arm (2, 4, internal Northwell data), 246 patients will be needed to be enrolled (123 in each arm) to have 80% power with a two-sided significance level of 0.05. Assuming a 20% drop out rate, we will need 308 patients in total. The primary analysis will be done in the mITT and per-protocol population. The SAF Population consisting of all randomized patients who received at least one dose of the study drug is also known as the mITT population. Reporting of the SAF population will be done according to the majority treatment received (as treated), whereas analysis of the mITT population will be analyzed according to randomization assignment. The Per Protocol (PP) Population will consist of all patients who received at least 80% of planned therapy and did not have any major protocol deviations. Planned therapy will be calculated as the duration in days that the subject received study treatment according to randomization arm divided by the duration of hospitalization after randomization, in days. Major protocol deviations can be assessed from the database and will include those patients that did not meet inclusion criteria or met exclusion criteria, permanently discontinued assigned study medication after randomization not due to an outcome event, and did not undergo the Day 10+4 lower extremity (LE) Screening Doppler compression ultrasonography (CUS).

9.3.8 Secondary Efficacy Analyses
The secondary outcomes described above will be analyzed using a combination of methods for continuous, ordinal, categorical and binary data.

9.4 Biomarker Analyses
N/A

9.5 Safety Analyses
Safety population: The SAF Population consists of all randomized patients who received at least one dose of the study drug. Reporting of the SAF population will be done according to the majority treatment received (as treated).

9.6 Data Safety Monitoring Board
An independent data safety monitoring board (DSMB) will actively monitor interim data to review the ongoing safety of patients and can make recommendations about early study closure or changes to the protocol. The DSMB members will include 3 voting members, 2 physicians with relevant medical specialty training and experienced in clinical trials research and 1 clinical trial statistician. All DSMB members must be free of both substantial intellectual and financial conflicts of interests. The DSMB chair reviews subject safety results every 2 weeks by group assignment, judges whether the overall safety of the project remains acceptable, has ongoing access to un-blinded information, and makes recommendations after discussion with the DSMB committee and including review of Interim Analysis results, about early study closure or changes to the protocol to the study Principal Investigator (PI) and Executive Committee, who has the responsibility to accept, reject or to modify DSMB recommendations. The DSMB
meeting frequency will be as follows ~25%, ~50%, ~75% and ~100% enrollment. Furthermore, the detailed operation of the DSMB is governed by a charter describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring) and requirements for reporting (Appendix G).
9.7 Executive Committee
There will be a study Executive Committee consisting of the study Principal Investigator as Chair and other study investigators, as well as up to 4 external members with expertise in antithrombotic trials. This Executive Committee will assist the study Chair in managing quality oversight of trial-related activities during the conduct of the clinical trial.

10 DATA INTEGRITY AND QUALITY ASSURANCE

10.1 Monitoring
The PI or designee will visit each site prior to enrollment and throughout the study duration to ensure safety and adherence to study protocols. The number of visits for any given site may vary based on site risk indicators. Study-related monitoring may also be done by internal and external regulatory agencies, including the IRB and OHRP. Study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements. Quality assurances for monitoring the local adjudication process for events may be used at the discretion of the DSMB Chair and Principal Investigator or designee, and if high variability is observed, additional review (e.g. central review of some events) may be conducted.
10.2 Data Collection

Subjects enrolled in this study will undergo laboratory testing as part of standard-of-care. The results of these tests will be collected, as indicated. Certain tests that are not necessarily part of standard-of-care will also be collected as part of this study, as indicated. Subjects will be made aware of and will be required to consent to additional procedures during the Informed Consent process. Detailed instructions for blood/NP swab sample collections will be in the laboratory manual provided to study sites.

10.3 Data Management

A data management plan specifying all relevant aspects of data processing for the study will be maintained with the regulatory documentation for this protocol. All data coding (SAEs, baseline findings, medication, medical history, etc.) will be done using internationally recognized and accepted abbreviations. Northwell Health has designed and implemented a HIPAA compliant COVID-19 DataMart data collection tool (see Appendix H) which will be utilized to obtain clinical data for COVID-19 patients within the health system in addition to the medical record.

10.4 Electronic Systems

Electronic systems that may be used to process data in this study will include:

- Biostatistics Randomization Management System (BRMS) – randomization
- REDCap – data collection CRF
- Statistical Analysis System (SAS) – statistical review and analysis

10.5 Study Documentation

10.5.1 Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded onsite on paper Case Report Forms (CRFs), and then transferred to REDCap by trained study staff. All required CRFs must be completed for every study subject. The PI will ensure the accuracy, completeness, and timeliness of the data and will provide his electronic signature upon review. Copies of paper CRFs will be retained as part of the study record and available for inspection by regulatory authorities. The electronic systems used for data management all employ an audit trail that will reflect any changes made to study records.

10.5.2 Record Retention and Storage

All essential study documents, including ICFs, source documents, CRFs, drug accountability records, and regulatory documentation will be stored in a locked office at the Center for Health...
Innovations and Outcomes Research at Northwell Health with access limited to approved study personnel only. All documents will be retained for at least 15 years following the completion or discontinuation of the study.

10.6 Operational Procedures

An ‘Investigator-Initiated Multicenter Coordinating Site’ will be established to coordinate study personnel working remotely and/or external to the Health System and monitor study tasks. These tasks will include but are not limited to the following: 1) track all data, 2) coordinate meetings (1x monthly or more as needed), 3) maintain regulatory documentation, 4) oversee study personnel and address staffing needs (if applicable). A Meta-Site Principal Investigator will be identified to oversee these tasks at each site.

The Main Principal Investigator will ensure the conduct of human subject research at each site involved in the Multicenter HSR Clinical Trial meets the requirements of 45 CFR 46/21 CFR 50 (Protection of Human Subjects), and 21 CFR 56 (Institutional Review Board). All Meta-Site Principal Investigator(s) and corresponding research staff members will attend an extensive Site Initiation Visit (SIV) prior to onboarding where the IRB approved protocol and all study related material will be discussed. Furthermore, prior to any study related activities at corresponding external research site(s) there will be a fully executed contract between both the Coordinating Center (i.e. Sponsor) and External Site(s) which will clearly address the responsibilities of the External Site and ensure the study will be conducted in compliance with federal regulations, all applicable state and local regulations, and ethical principles governing research involving human subjects. The roles and responsibilities of each party will be outlined in the External Agreement Contract (Appendix J).

As per [21CFR56.114] the External Sites will rely upon the review of their own qualified Institutional Review Board as outlined in the External Agreement Contract (Appendix J). Due to the nature of the COVID-19 pandemic, all external sites will utilize their local site-specific IRB, which will be responsible for reviewing the proposed research and activities at that site [21 CFR 56.111, 45 CFR 46.111].

The Main Principle Investigator will ensure each external site(s) maintain a comprehensive study management plan which will outline the following:

- **Compliance plan that details:**
  - Actions for ensuring and monitoring protocol and regulatory compliance
  - Actions to be taken in the event unanticipated problem involving risks to subjects or others, and
  - A process for receipt and evaluation of protocol deviations and exceptions.

- **Study management plan that addresses:**
  - Documentation of initial and continuing IRB review for each site,
  - Confirmation that each external institution has a Federal-Wide Assurance on File with Office of Human Research Protection (if applicable);
  - Initial and continued training of sites,
  - Method for assuring that all sites have and implement the most current
version of study documents (including protocols, investigator’s brochure (if applicable), Informed consent forms and case report forms), and

- The collection and security of data (External REDCap Setup)
A process for handling the commercial product (responsibility of site-specific pharmacy)

A Data Monitoring Plan, Data Safety Monitoring Board or Committee (Appendix G),

A process for evaluating and reporting of serious adverse events (SAEs) from sites, and

A plan to monitor the conduct and progress of the human subject research study (which includes a plan for the management of noncompliance).

Documentation of compliance with the responsibilities mentioned above will be maintained at each corresponding external site(s) and readily available to Coordinating Center (as requested). The main Study PI will receive and confirm IRB approvals from each site prior to each site starting study subject enrollment. Each site will be responsible for IRB/Institutional approval of the protocol from the corresponding site-specific local IRB. The main PI will be responsible for collecting the approval documents and ensuring it is readily available for review as per regulatory compliance. Furthermore, the main Study PI and lead research team will coordinate a mandated site initiation visit (SIV) for all study sites both internal and external prior to study activation.

There shall be no fees, charges or other payments made or payable by Sponsor to Participating Institution for conducting this Trial or otherwise in connection with the Clinical Trial. Participating Institution shall be responsible for funding its own activities, including those of Site Investigator, in the conduct of the Clinical Trial (Appendix J).

In the event of a degradation of system-wide resources and/or significant staffing reduction due to the nature of the COVID-19 pandemic, every effort will be made to collect data as described in this protocol. A majority of data will be collected from the COVID-19 Data Mart and/or REDCap Database (Secure setup for External Users) established and maintained by the Center for Health Outcomes Research at Northwell Health. Protocol deviations will be reported as feasible. Subjects will continue to receive care while hospitalized, however will not be prioritized over non-study participants for available equipment and/or other resources.

Of note, regardless of study participation, the decision for ventilator support is based on the clinical decision making of the care team.

11 PUBLICATION POLICY

11.1 Publication and Public Disclosure of Clinical Trial Information
This study and results will be made publicly available on ClinicalTrials.gov. Processes for publications resulting from this study will be outlined separately in the Executive Committee Charter.

12 ETHICS AND ADMINISTRATIVE INFORMATION
12.1 Good Clinical Practice Statement
It is the responsibility of the PI and all study personnel to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.
12.2 Confidentiality

All appropriate measures will be taken to ensure that the anonymity of each subject is maintained. Subjects will be identified by an alphanumeric code only on CRFs and other related documentation. Source documentation that may not be coded will be kept confidential.

12.3 Informed Consent

It is the responsibility of the PI or other IRB-approved study personnel to obtain informed consent from each subject or a legally authorized representative (LAR) prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the potential subject in language that he/she can understand. The following procedures are based on the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic and will be applied to this study.

For patients that are able to sign for themselves:

- Healthcare worker who enters the room (can be the investigator, but does not have to be) provides the patient with a copy of the consent form.
- If the consenting investigator is in the room with the patient during the consent process, the patient and the consenting investigator will sign the consent form. Witness signature will be waived. The consent process will be documented in an enrollment note as per Northwell Policy GR089.
- If direct communication with the patient is not feasible due to isolation, the investigator obtaining consent from outside of the room will arrange a three-way call or video conference with (a) the patient, (b) a witness, and (c) if desired by the patient, additional participants (e.g., next of kin).
  - The consent process will include the following steps:
    - Each attendee on the call or video conference identifies him/herself (include name and role/relationship to patient).
    - Investigator reviews the consent form with the patient and answers any questions that occur during the conversation.
    - Witness verbally confirms that patient’s questions have been answered. If the healthcare worker in the room serves as the witness, the healthcare worker must sign the consent form as witness to the consent process.
    - Investigator asks the patient to confirm that the patient is willing to participate in the trial and to sign the consent document while the witness is present or listening on the phone or video conference.
    - Patient verbally confirms that s/he would like to participate in the trial and patient signs and dates the consent form.
    - The signed consent form is collected from the patient room following infection control protocols. More specifically, pen used by patient to sign the consent form is thrown away and consent form signed by the patient is placed in a biohazard bag and then in a clean bag. Investigator will sign the consent form once the paper copy becomes
available and ensure that the fully signed consent form is filed in the patient’s record.

- If it is not possible to collect the consent form due to contamination of document by infectious material, one of the following will be done:
  - The Investigator and witness will sign and date a copy the consent form and provide individual attestation using the COVID-19 Witness Attestation form
& COVID-19 Investigator Attestation form that the patient agreed to
participate in the study and signed the informed consent form.

OR

• The healthcare worker in the room (in her/his capacity as witness) can
  photograph the signature page of the consent form as signed by the patient
  and witness and forward to the investigator to print and place in the patient’s
  record. An attestation (using the COVID-19 Investigator Attestation form) by
  the person entering the photograph in the study record must indicate how the
  photograph was obtained and confirm that it is a photograph of the informed
  consent form signed by the patient.

When informed consent is to be obtained from a Legally Authorized Representative (LAR), who is
not present due to isolation rules, and have access to email:
• The investigator will contact the LAR on the phone and request an email address to email
  a copy of the informed consent form.
• Consent form will be emailed to the LAR for review during consent conversation with
  the investigator.
• The investigator obtaining consent arranges a three way call or video conference with (a)
  the patient’s LAR, (b) an impartial witness, and (c) if desired by LAR, additional participants
  (e.g., patient’s next of kin)
  • The consent process will include the following:
    • Each attendee who is on the call or video conference
      identifies him/herself (include name and role/relationship to
      patient)
    • Investigator reviews the consent form with the LAR and answers
      any questions that occur during the conversation
    • Witness verbally confirms that LAR's questions have been answered
    • Investigator asks the LAR to confirm that the LAR is in agreement with
      patient’s participation in the trial while the witness is listening on the
      phone or video conference
    • LAR verbally confirms that s/he would like the patient to participate
      in the trial and LAR signs and dates the consent form (if feasible).
• Investigator and impartial witness will sign and date a copy of the consent form.
• Investigator will ask LAR to:
  • Sign and date the LAR’s copy of consent form and email back a scanned copy.
  OR
  • Take a photograph of the signature page of the LAR’s signed and dated consent
    form and forward to the investigator. The photo of the LAR’s signed and dated
    signature page of the consent form will be printed and placed in the patient’s
    record along with the paper consent form signed by the investigator and witness.
  OR
Send an email response to the investigator indicating agreement to allow patient’s participation in the clinical trial (if they cannot email or scan the signed consent form). The Investigator and witness will provide individual attestation that the LAR is in agreement with the patient’s participation in the study (using the COVID-19 Witness Attestation form & COVID-19 Investigator Attestation form). In addition, the investigator will send, through certified mail, a copy of the consent form to the LAR and ask for the LAR to sign and date the consent and send it back by mail for confirmation of signature.
• The enrollment note must include a description of the consent process followed and if applicable, will indicate why the original signed document was not retained (using COVID-19 Enrollment Note).

When informed consent is to be obtained from a Legally Authorized Representative (LAR), who is not present due to isolation rules AND does not have access to email or one does not exist, verbal consent can be obtained as follows:
• The investigator will contact the LAR on the phone and inform him/her that a three way call or video conference with (a) an impartial witness, and (b) if desired by the LAR, additional participants (e.g., patient’s next of kin) will be conducted to discuss the study.
• During the consent conversation, investigator will review the consent form with the LAR and any additional participants.
• The consent process must include the following:
  • Each attendee who is on the call or video conference identifies him/herself (include name and role/relationship to patient)
  • Investigator reviews the consent form with the LAR and answers any questions asked during the conversation
  • Impartial witness verbally confirms that LAR’s questions have been answered
  • Investigator asks the LAR to confirm that the LAR is in agreement with patient’s participation in the trial while the impartial witness is listening on the phone or video conference
  • LAR verbally confirms that s/he would like the patient to participate in the trial.
• Following the LAR’s verbal confirmation that he/she agrees to allow patient’s participation in the clinical trial, the investigator will mail a copy of the consent form to the LAR and ask for the LAR to sign and date the consent and send it back by mail for confirmation of signature.
• Investigator and impartial witness will sign and date a copy of the consent form and each will provide attestation (using the COVID-19 Witness Attestation form & COVID-19 Investigator Attestation form) that the LAR is in agreement with the patient’s participation in the study.
• The enrollment note will include a description of the consent process and if applicable, should indicate why the signed document was not retained (using the COVID-19 Enrollment Note).

Patients with Limited English Proficiency (LEP) will not be excluded from this study. Informed Consent will be obtained in this case following the procedures detailed above, using an impartial interpreter and a short form translated into the patient’s preferred language, and in accordance with Northwell Health policy GR089 for obtaining informed consent for patients with Limited English Proficiency.
12.4 Regulatory Compliance

The Northwell Health Institutional Review Board (IRB), as described in ICH guidelines for GCP, will provide regulatory oversight of this clinical study within the Northwell Health System. The IRB will review and approve:

- The protocol, Informed Consent Form, and advertising materials,
- Amendments or modifications to the protocol or ICF before implementation,

In addition, the IRB will be informed of any event likely to affect the safety of patients or the conduct of the study. Records of the IRB review and approval of all study documents will be kept on file by the PI.

All External Site(s) will refer to their local site-specific (IRB) as described in ICH guidelines for GCP, who will provide regulatory oversight of this clinical study at their local institution.

12.5 Protocol Deviations

Major and minor protocol deviations will be reported according to institutional policy.

12.6 New Information Affecting the Conduct of the Study
If new information affecting either the conduct of the study or the initial risk/benefit assessment becomes available, this protocol will be amended as needed and submitted for IRB review. Subjects will be informed and required to provide informed consent.

12.7 Protocol Amendments

All amendments or modifications to this protocol will be reviewed and approved by the IRB prior to implementation. In the event that a modification is required in an emergency situation, the IRB will be notified immediately.

12.8 Study Termination

The sponsor, investigator, and/or regulatory agencies have the right to terminate the study prematurely on the basis of safety, efficacy or futility.
13 REFERENCES


[17] Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AYY. Management of challenging cases of


Patients with cardiovascular disease do worse with COVID-19 and there is an increased frequency of CVD-associated SAEs associated with the coronavirus itself or with antivirals and other treatment modalities (myocarditis, acute coronary syndromes, cardiac arrhythmias, cardiogenic shock, and venous thromboembolism). There is also a worse prognosis for patients with very elevated D-dimer (>6X ULN) although mechanisms are incompletely understood: Proposed mechanisms include coagulopathy/DIC, cytokine storm, and presence of microthrombi. There may be issues of hepatic enzyme dysfunction (CYP3A4 inhibition), with the use of certain antivirals (Lopinavir/Ritonavir), which results in impaired metabolism of antithrombotics. Lastly, recent clinical data supports aggressive prophylactic-to-intermediate dose pharmacologic thromboprophylaxis with low molecular weight heparin in hospitalized COVID-19 patients with severe illness as well as extended thromboprophylaxis in high VTE risk patients (IMPROVE VTE score 4 or more, advanced age, elevated D-dimer). Key points:

- Do NOT stop antithrombotics in COVID-19 patients
- Consider changing clopidogrel/ticagrelor to prasugrel in patients on Lopinavir/Ritonavir or consider P2Y12 monitoring
- Careful consideration of apixaban/rivaroxaban in patients on Lopinavir/Ritonavir or consider dabigatran or dose adjusted warfarin
- Also consider substituting argatroban IV for UFH IV for device associated anticoagulation issues. Empiric use of treatment dose heparin (IV UFH/LMWH) or use of systemic tPA should be studied in a randomized trial setting
- For hospitalized non-ICU patients, thromboprophylaxis in patients with CrCl > 15ml/min and BMI < 30 using enoxaparin 40mg SQ QD; with BMI > 30 using enoxaparin 40mg SQ BID; in patients with CrCl < 15ml/min or RRT and BMI < 30 use UFH 5000U SQ BID or TID; in patients with CrCl, 15ml/min or RRT and BMI ≥ 30 use UFH 7500U SQ BID or TID
- In ICU patients, as above but also use multimodal prophylaxis with mechanical methods (IPCs).
- Extended thromboprophylaxis with enoxaparin 40mg SQ QD or rivaroxaban 10mg PO QD for 31 – 39 days’ post-discharge in patients with an IMPROVE VTE score of ≥ 4 or age > 60yrs and/or elevated D-dimer (> 2X ULN).
14.2 Appendix B

ISTH Sepsis Induced Coagulopathy (SIC) Score

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td><strong>Platelets, K/µL</strong></td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>2</td>
</tr>
<tr>
<td><strong>INR</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>&gt;1.7</td>
<td>2</td>
</tr>
<tr>
<td><strong>D-Dimer, ng/mL</strong></td>
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<td></td>
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<td></td>
<td>&gt;4000</td>
<td>3</td>
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<tr>
<td><strong>Fibrinogen, mg/dL</strong></td>
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<tr>
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<td>&lt;100</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix C

Duplex Doppler Screen

Imaging for screening or suspected DVT [19–21]:

Lower extremity Duplex screening compression ultrasonography will be done at Hospital Day 10+4 or sooner at the time of hospital discharge using standardized screening methods. Confirmatory lower extremity ultrasound of symptomatic DVT or asymptomatic screening of lower extremity DVT is recommended using full duplex Doppler compression ultrasonography of the entire extremity venous system. Where resource constraints or local institutional policies preclude use of full ultrasound, point-of-care ultrasound using two-region compression can be substituted and has shown reasonable accuracy.

Full duplex ultrasound is the preferred venous ultrasound test for the diagnosis of DVT. This includes compression of the deep veins from the inguinal ligament to the ankle (including posterior tibial and peroneal veins in the calf), right and left common femoral vein spectral Doppler waveforms (to evaluate symmetry), popliteal spectral Doppler, and color Doppler images. Compression is performed at 2-cm intervals.

A point-of-care ultrasound consisting of a limited evaluation with compression from thigh to knee (extended compression ultrasound) is appropriate when full duplex US is not available in a timely manner. Extended compression point of care ultrasound is performed with compression from the inguinal ligament extending through the popliteal vein to the calf vein confluence at 2 cm intervals. Extended compression, if possible, is favored over 2-region compression because isolated femoral vein DVTs may be missed. However, in the COVID pandemic, two-region (two-point) compression can be substituted. Two-point compression point of care US is performed with the first region of compression extending from 1 to 2 cm above to 1-2 cm below the saphenofemoral junction. The second point of compression begins at the origin of the popliteal vein extending to the calf vein confluence. Acute venous thrombosis should be defined as lack of compressibility, but the thrombus is soft and deformable with increasing probe pressure. Chronic post-thrombotic change is seen as rigid, non-compressible intraluminal material which is nondeformable with increasing probe pressure.
### Quick SOFA Score

<table>
<thead>
<tr>
<th>Assessment</th>
<th>qSOFA score</th>
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</thead>
<tbody>
<tr>
<td>Low blood pressure (SBP ≤ 100 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>High respiratory rate (≥ 22 breaths/min)</td>
<td>1</td>
</tr>
<tr>
<td>Altered mentation (GCS ≤ 14)</td>
<td>1</td>
</tr>
</tbody>
</table>
### 14.5 Appendix E

**The 7 Factor IMPROVE VTE RAM *(18)*

<table>
<thead>
<tr>
<th>VTE Risk Factor</th>
<th>Points for the Risk Score</th>
</tr>
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<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Thrombophilia**</td>
<td>2</td>
</tr>
<tr>
<td>Current lower limb paralysis or paresis***</td>
<td>2</td>
</tr>
<tr>
<td>Cancer****</td>
<td>2</td>
</tr>
<tr>
<td>Immobilization*****</td>
<td>1</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
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</tr>
</tbody>
</table>

**Abbreviations:**

IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; VTE, venous thromboembolism; RAM, risk assessment model; ICU, intensive care unit; CCU, coronary care unit.

*A score of 0-1 constitutes low VTE risk; a score of 2-3 constitutes moderate VTE risk; a score of 4 or more constitutes high VTE risk.*

**A congenital or acquired condition leading to an excess risk of thrombosis (i.e. FV Leiden, prothrombin gene mutation, Protein S, C or antithrombin deficiency, antiphospholipid syndrome, hyperhomocysteinemia).**

***Leg falls to bed by 5s, but has some effort against gravity (from NIH stroke scale).***

****May include active cancer (excluding non-melanoma skin cancer) or a history of cancer within 5 years.*
Strict definition is complete immobilization confined to bed or chair ≡ 7 days; modified definition is complete immobilization with or without bathroom privileges ≡ 1 day.
14.6 Appendix F

**Study Flow Chart and Events Schedule**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening (Up to 72 hours before randomization)</th>
<th>Day 0 (Day of randomization)</th>
<th>Hospital Day 10 + 4 or discharge</th>
<th>Day 30 ± 2</th>
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<td>Study Labs</td>
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<td>Concomitant Medications*</td>
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<td>Use of mechanical Thromboprophylaxis</td>
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<td>Clinical scores**</td>
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<td>Secondary Outcome Assessment/SAEs</td>
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<td>Screening LE Doppler CUS</td>
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</table>

*including unblinded investigational agents for COVID-19

** SIC score, Quick SOFA score, IMPROVE VTE Risk score,
Data Safety Monitoring Board Charter

Protocol Title: Systemic Anticoagulation with Full Dose Molecular Weight Heparin (LMWH) vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients (HEP-COVID Trial)

Protocol Number: 20-0340

Sponsor: Feinstein Institutes for Medical Research and Northwell Health

Version Date: 20200509
Version Number: 0.08
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8. STUDY DESIGN
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9. STUDY TREATMENTS
   9.1. Study Drugs
   9.2. Preparation
   9.3. Administration

Our hypothesis is that sick hospitalized COVID-19 patients receiving therapeutic doses of heparin (LMWH) during hospitalization will show a reduction of the primary and secondary endpoints that are associated with a prothrombotic state within 30 days of their hospital admission.

Enoxaparin injection and unfractionated heparin are anticoagulant medications approved for use to prevent thromboembolic complications. Both medications as per as protocol are approved for use in hospitalized patients.

Enoxaparin injection is available in pre-filled syringes in 40mg, 60mg, 80mg, 100mg, 120mg, or 150mg vials. Unfractionated heparin injection is available in pre-filled syringes or in multi-dose vials.
At Hospital Day 10 + 4 or sooner at the time of hospital discharge, there will be a lower extremity Duplex screening compression ultrasonography of the entire extremity venous system. Where resource constraints or local institutional policies preclude use of full ultrasound, point-of-care ultrasound using two-region compression can be substituted and has shown reasonable accuracy (Appendix C). There will also be an assessment of the primary efficacy, principal safety, and secondary outcomes.

At Day 30 ± 2, there will be an assessment of the primary efficacy, principal safety, and secondary outcomes via a face-to-face or telephonic visit. At Hospital Day 10 + 4 or sooner at the time of hospital discharge, there will be a lower extremity Duplex screening compression ultrasonography of the entire extremity venous system. Where resource constraints or local institutional policies preclude use of full ultrasound, point-of-care ultrasound using two-region compression can be substituted and has shown reasonable accuracy (Appendix C). There will also be an assessment of the primary efficacy, principal safety, and secondary outcomes.
A single interim analysis is planned after the primary outcome status is observed on half (123) of the randomized patients. The interim analysis will allow early termination for evidence of efficacy if the absolute risk reduction (ARR) is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate dose group.

Assuming a 40% relative risk reduction in the primary efficacy outcome with LMWH treatment (4) and an incidence of the primary efficacy endpoint of 42% in the usual medical care arm (2, 4, internal Northwell data), 246 patients will be needed to be enrolled (123 in each arm) to have 80% power with a two-sided significance level of 0.05. Assuming a 20% drop out rate, we will need 308 patients in total. The primary analysis will be done in the per-protocol population. The per protocol analysis set will consist of all patients who received at least 80% of planned therapy. The safety analysis will consist of all patients who received at least one dose of study medication.

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INTRODUCTION

This Charter is for the Independent Data Safety Monitoring Board (DSMB) for the Northwell Health study entitled Systemic Anticoagulation with Full Dose Low Molecular Weight Heparin (LMWH) vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients (HEP-COVID Trial) (Protocol # 20-0340). The Charter will define the organization and primary responsibilities of the DSMB, DSMB related responsibilities of the Executive Committee, Northwell Health, and CPC Clinical Research (Academic Research Organization – ARO). This Charter will also define the purpose and timing of DSMB meetings, provide the procedures for ensuring confidentiality and proper communication, outline the statistical monitoring guidelines to be implemented by the DSMB, and describe the content of the open and closed reports that will be provided to the DSMB. Stopping guidelines and unblinding procedures are also described, as applicable.

The DSMB is the primary outcome data and safety advisory group for this study. The DSMB chair reviews subject safety results every 2 weeks by group assignment, judges whether the overall safety of the project remains acceptable, has ongoing access to un-blinded information, and makes recommendations about early study closure or changes to the protocol to the study Principal Investigator (PI) and Executive Committee, who has the responsibility to accept, reject or to modify DSMB recommendations.
ORGANIZATION

Composition of the DSMB
The DSMB members include 3 voting members, 2 physicians with relevant medical specialty training and experienced in clinical trials research and 1 clinical trial statistician. All DSMB members must be free of both substantial intellectual and financial conflicts of interests. As such, committee members may not participate in the study as principal or co-investigators, or as study physicians. All potential conflicts of interest must be disclosed by potential DSMB members prior to appointment. Whether a potential conflict of interest is, in fact, substantive and disqualifying will be determined by the Executive Committee. Per FDA guidance, any potential conflicts of interest that are not thought to impede objectivity and thus would not preclude service on the DSMB, should be disclosed to all DSMB members. DSMB Members are as follows:

- James Douketis, MD (Chair)
- Sam Schulman, MD (Member)
- John Kittelson, PhD (Statistician Member)

At the discretion of the DSMB, additional experts may be consulted as needed with prior Sponsor approval.

Selection of DSMB Members
The DSMB Chair will be selected by the chair of the Executive Committee. CPC may participate in DSMB Chair recommendations if requested by the Executive Committee. The DSMB Chair will provide recommendations for selection of other DSMB members with the assistance of the Executive Committee or CPC if requested. Members will be subsequently approved by the DSMB Chair and Executive Committee. In the event that a member is unable to continue participation on the DSMB, the DSMB Chair will recommend a replacement to the Executive Committee. If the DSMB Chair is unable to continue participation on the DSMB, the Executive Committee will select a new Chair.
RESPONSIBILITIES OF THE DSMB

The DSMB is responsible to the Executive Committee for oversight of accumulating study outcome data for assurance of subject safety and trial integrity.

A. The DSMB Chair is responsible for:
   - Chairing all meetings for the duration of the trial.
   - Being responsive to subject safety issues throughout the study. The DSMB Chair will review safety data every 2 weeks to identify any safety concerns with the option to call a meeting as needed of the full committee. The DSMB Chair will chair all full-committee meetings including the meeting to review and make interim continuation recommendations based on the results of the interim analysis.
   - Sending an e-mail to the study PI every 2 weeks noting their review and if any safety concerns were identified. The Study PI will inform the Executive Committee of the recommendations from the DSMB following receipt of the e-mail from the DSMB chair.
   - Establishing the format of safety data presentation.
   - Establishing priority and scheduling of teleconference meetings and working with the DSMB coordinator to resolve scheduling conflicts.
   - Facilitating discussion, integrating differing points of view and moving the other DSMB members toward consensus on recommendations provided to the Sponsor.
   - Communicating the DSMB recommendation to the PI and Executive Committee at the conclusion of each meeting during a concluding open session. This can be by e-mail immediately following each meeting with a letter of that recommendation to follow.
   - Approving open and closed session minutes within 1 day of meeting.
   - Overseeing the overall function of DSMB including attendance at teleconference meetings.

B. The DSMB (including the DSMB Chair) are responsible for:
   - Attending scheduled DSMB teleconference meetings.
   - Maintaining confidentiality as outlined in the member’s contract.
   - Disclosing any potential conflicts of interest (inclusive of any that are not thought to impede objectivity and thus would not preclude service on the DSMB) to all DSMB members.
   - Providing input to the DSMB Charter and attachments.
   - Providing input and approving the contents of the open and closed DSMB reports (i.e. safety and related parameters to be monitored), frequency of Committee monitoring reviews, methods for review, statistical methodologies, quorum of Committee members, and establishing criteria for making recommendations to the Executive Committee.
   - Reviewing accumulating data generated by the study and safety events on a periodic basis and the results of the interim statistical analysis. The DSMB will make one of the following actions to the Sponsor:
     i. Continue the study according to the protocol and any related amendments.
     ii. Modify the study protocol. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency of visits for safety monitoring, alterations in study procedures, changes in duration of observation, and follow up.
     iii. Discontinue the study (with provisions for orderly discontinuation in accord with good medical practice).
   - Documenting and approving the procedures defined above.
RESPONSIBILITIES OF EXECUTIVE COMMITTEE

The Executive Committee is responsible to the DSMB for the following:

A. Approving the selection of the DSMB Chair and other DSMB members.
B. Reviewing and approving the DSMB Charter.
C. Reviewing and approving the formal stopping guidelines outlined in the DSMB Charter.
D. Responding to requests from the DSMB for additional information.
E. Responding to DSMB recommendations and concerns in a timely fashion.
RESPONSIBILITIES OF SPONSOR (FEINSTEIN RESEARCH INSTITUTES AND NORTHWELL HEALTH)

The Sponsor is responsible to the DSMB for the following:

A. Making adequate resources available to the DSMB as required to carry out its designated functions, including provision of a copy of the current protocol (IRB approved); copies of any in-study expedited safety reports submitted to regulatory authorities; and pertinent efficacy and safety data from other trials involving the use of the study drug in this patient population.

B. Ensuring data on trial conduct are provided to the PI and EC as scheduled. This includes blinded operation reports on patient demographics, SAEs, and endpoints.

C. Responding to requests from the DSMB for additional information.

D. Communicating all pertinent regulatory information to individuals/entities that will vary depending on the specific circumstances, but may include the individual Investigators, IRBs, NIH, and the US Food and Drug Administration (FDA).
RESPONSIBILITIES OF CPC

CPC is responsible for the organization and management of the DSMB activities and materials including the following:

A. Providing a DSMB support team inclusive of a DSMB Coordinator and a DSMB Reporting Biostatistician.
B. Assisting the DSMB Chair with considerations in the selection of DSMB members, when requested.
C. Collecting, reviewing, and approving DSMB member documents (CVs, Contact Information, and Conflict of Interest Statements).
D. Developing and circulating the draft of the DSMB charter for review and approval.
E. Circulating the draft of the open and closed DSMB report template (if not an appendix to the DSMB Charter) for review and approval.
F. Providing meeting support to the DSMB Chair including:
   - Assisting with scheduling;
   - DSMB Coordinator will draft (open and closed) agendas and minutes (open meeting minutes will include the DSMB recommendations from the closed session);
   - DSMB Coordinator and Reporting Biostatistician will attend all DSMB Open and Closed session meetings;
   - Distributing supporting documents (i.e. reports, protocol, etc.).
G. Generating the open and closed DSMB reports from the most current study data.
H. Communicating requests for information from the DSMB to the Sponsor.
I. Maintaining all DSMB member and meeting documentation in the Trial Master File (closed session documentation will be maintained separately and kept confidential for the duration of the study and will be transferred to the Trial Master File following database lock).
J. Overseeing and processing of study data transfers and security by drafting and finalizing applicable Data Transfer Agreements (DTAs).
K. Monitoring project timelines and deliverables.
RESPONSIBILITIES OF DATA MANAGEMENT

Feinstein Research Institutes and Northwell Health will be responsible for data management through the Biostatistics Randomization Management System and REDCap and will be responsible for the following:
A. Participating in drafting and following the Data Transfer Agreements (DTAs) established by CPC Clinical Research.
B. Coding SAE terms to MedDRA
C. Securely transferring required coded AEs and SAEs clinical study data for the creation of unblinded closed DSMB reports biweekly to accommodate DSMB chair review every two weeks for the duration of the study.
CONDUCT OF DSMB MEETINGS

Meeting Frequency
The frequency at which the DSMB convenes ultimately depends on actual subject enrollment, and safety event rates and perceived risk of the investigational products. The meetings will be structured as follows:

- Initial meeting – to approve charter and tables
- Every 2 week Chair review of data for safety with provision to trigger a full meeting if needed,
- ~25% enrollment – full safety meeting,
- ~50% enrollment – full safety meeting,
- ~75% enrollment – full safety meeting,
- 100% enrollment – final meeting.

The review of the interim analysis will occur when approximately half of the subjects have completed the day 30 primary endpoint assessment. The interim analysis meeting may be scheduled in conjunction with one of the four safety meetings or may require a separate meeting. Thus, there will be 4 or 5 formal meetings in addition to the Chair looking at safety data every 2 weeks. The Chair can trigger a meeting of the full committee if warranted by safety, accrual or other study conduct concerns. The Chair will send an e-mail to the trial PI every 2 weeks confirming review and noting any concerns. The PI will inform the EC of the Chair’s review and any concerns. It is not anticipated this committee will need to meet face to face.

If the DSMB Chair is unavailable for a particular 2-week safety review, the Chair can appoint one of the members of the DSMB to perform that function. However, the Chair must be present for all formal DSMB meetings including the review of the Interim Analysis.

Quorum
There are three members of the DSMB including the Chair. The Chair and at least one other member of the DSMB must be present at a DSMB meeting to achieve quorum. The interim analysis meeting must be attended by all DSMB members. If a DSMB member is unable to attend a scheduled teleconference meeting they may submit their comments to the DSMB Chair or DSMB Coordinator by e-mail prior to the meeting and those comments would count toward the quorum.

Voting
DSMB members vote on all recommendations to be submitted to the Executive Committee. To vote on a recommendation, the Chair and at least one other member of the DSMB must be participate in the teleconference. A simple majority of voting passes a proposal, motion or recommendation to the Executive Committee. In the event of a split vote, the DSMB Chair will determine the passage of a proposal, motion, or recommendation.

DSMB Charter Meeting
The initial meeting of the DSMB will be a Charter Meeting wherein the final draft of this Charter should be reviewed and finalized. Additional input on the protocol and analytic plan, sample informed consent form, data collection instruments, other important trial documents or any suggestion for modification to the Sponsor may be made prior to the first meeting of the committee. During the initial meeting, regulatory considerations may be discussed prior to the review of any study data.

Discussion may also include:
- Standard operating procedures for the role and function of the DSMB.
- Scheduling of meetings.
- Format and content of the open and closed DSMB reports that will be used to present data at future meetings.
Timing of the delivery of the open and closed DSMB reports to the DSMB members prior to the meeting.

Handling of meeting minutes.

Confirming or making recommendations to the plan for monitoring the data throughout the trial.

Confirming or making recommendations to the stopping criteria in the interim analysis plan.

**Meeting Format**

Meetings will consist of beginning open session, a closed session, and a concluding open session. During the initial open session of a meeting, an Executive Committee representative, CPC representative, or invited guest(s) may be asked to discuss study-specific issues or address questions from DSMB members. Information discussed during the open session excludes discussions of aggregate safety or efficacy summaries by treatment group. Discussions may be based on the contents of the open report or other study information such as site operations or screen failure reasons without treatment-aggregated data.

Discussions of the study data by treatment group will occur during the closed session, which will be attended by the DSMB members, the DSMB Coordinator and the DSMB Reporting Biostatistician. Information discussed during the closed session includes safety data and may include efficacy data and the interim statistical analysis. Information and discussion during the closed sessions will remain strictly confidential until database lock.

At the conclusion of the closed session the open meeting participants will be called back to the teleconference to receive the recommendations of the DSMB.

Microsoft Teams will be used for all teleconferences. Open and closed session attendees will be monitored by the DSMB Support Team to ensure the confidentiality of the various meeting sessions.

**Meeting Minutes**

Meeting minutes will be prepared by the DSMB Coordinator under the direction of the DSMB Chair for each meeting of the DSMB. Two sets of meeting minutes will be prepared: open and closed minutes.

The open minutes will describe the proceedings in the beginning and concluding open session of the DSMB meeting and will summarize the recommendations by the DSMB. The open minutes will be distributed to the Sponsor, DSMB members and other specified meeting attendees within approximately 1 business day of the meeting. Closed session meeting minutes will be circulated to the DSMB members within approximately 3 business days for approval. The DSMB Coordinator will keep these meeting minutes confidential for the duration of the study and will transfer to the Trial Master File following database lock.

**Procedures for Submitting Recommendations**

Because of the frequency of DSMB meetings the recommendations will be delivered verbally during the concluding open session of each meeting. Written documentation of the recommendations will be recorded in the open meeting minutes. The Sponsor has the responsibility to communicate recommendations to the individual investigators, IRBs and regulatory authorities, if required.
REPORTING AND ANALYSES

DSMB Blinding Status and Unblinding Procedures
This is an open-label study. The Sponsor, Executive Committee, site investigators, and DSMB may be aware of individual subject treatment assignments. However, the closed DSMB Closed Reports and minutes will be kept confidential to the DSMB during the course of the trial and will not be made available to the Sponsor until the trial has completed.

Open and Closed DSMB Reports
Mock tables, listings, and figures (TFLs) comprising the DSMB report contents will be developed and approved by the DSMB separate from this Charter and may be modified throughout the course of the study to meet DSMB needs. The open DSMB report will be available to attendees of the open DSMB session and will present study data overall without regard to treatment assignment such as:

- Trial enrollment status, overall and by participating site.
- Protocol deviations.
- Summary of baseline characteristics of overall study population.
- Summary of medical history of overall study population.
- Concomitant medication usage.
- Summary of serious treatment emergent adverse events.

The closed DSMB report will contain all tables provided in the open report, but data will be presented by treatment group in an unblinded fashion with the treatment codes reported separately to the DSMB. The closed report may additionally contain safety or interim analyses as specified in this Charter or an interim analysis plan. The closed report will be kept confidential to the DSMB and DSMB support team members who attend the closed DSMB session until the trial is complete.

Interim Analysis and Stopping Guidelines
There will be one formal pre-planned interim analysis (IA) to assess for early efficacy and futility, which will be performed when the primary outcome status (the primary clinical endpoint a composite of venous thromboembolism, arterial thromboembolism, and all-cause mortality measured at Day 30 +/- 2) is evaluable in approximately half of the randomized subjects (n=123). The interim analysis is anticipated to occur at or before the time when approximately 60% of subjects have been enrolled.

Details of the IA decision criteria for efficacy and futility of the primary clinical endpoint are described in the Interim Analysis Plan (attached) and is referenced in the study protocol. The IA will allow for early termination of the study for evidence of efficacy if the absolute risk reduction is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate dose group. The trial will allow for early termination of the study for futility if the risk of an efficacy event is larger with the therapeutic dosing than with the prophylactic dosing at IA. The Interim Analysis will be performed by CPC and reported to the DSMB for their review. The DSMB will then forward a recommendation to the Study PI and Executive Committee. Factors, in addition to the IA result, will be considered when making the recommendation following the IA meeting. The DSMB will assess efficacy, futility, safety and quality of trial conduct at the time of the IA.

Review of Adverse Events and Serious Adverse Events
Adverse Events (AEs) and Serious adverse events (SAEs), as defined by the study protocol, will be reviewed by the DSMB at scheduled DSMB meetings as provided in the closed DSMB report.
The Principal Investigator and Sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after initial receipt of information.

The DSMB will review unblinded data on determined AEs and SAEs at each DSMB meeting, as provided in the DSMB report.
13. TERMINATION

The DSMB shall have concluded its activities and oversight responsibilities when, after closure of new enrollment on the study under its purview as per this Charter, all of the following criteria are met:

- All enrolled subjects have completed their participation in the study;
- The final DSMB meeting has occurred for review of the cumulative data acquired on said subjects, as provided by the Sponsor/designee to the DSMB Reporting Biostatistician for inclusion in the DSMB report template;
- Any outstanding requests for information or clarification by the DSMB have been met to the satisfaction of the DSMB chair.

Documentation of conclusion of DSMB activities and oversight responsibilities will be made in the minutes of the final DSMB meeting, unless outstanding issues remain, in which case closure of these issues and conclusion of DSMB activities and oversight responsibilities will be documented via letter from DSMB Chair to Sponsor.

Should the Sponsor terminate the DSMB prior to the aforementioned criteria for termination having been met, the DSMB Chair will document this in a letter to Sponsor, and regulatory agencies (as appropriate), that the DSMB has been prematurely terminated by the Sponsor.
## DSMB MEMBERSHIP

<table>
<thead>
<tr>
<th>Name</th>
<th>James Douketis, MD</th>
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</table>
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<tr>
<th>Name</th>
<th>Alex Spyropoulos, MD, FACP, FCCP, FRCPC</th>
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</table>
| **Title**                 | Professor of Medicine – The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell  
                                 Professor – The Center for Health Innovations and Outcomes Research – The Feinstein Institute for Medical Research  
                                 System Director – Anticoagulation and Clinical Thrombosis Services |
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                                 New York, NY 10075 |
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<th>Dimitrios Giannis, MD</th>
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</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Thrombosis Research Fellow, Feinstein Institutes for Medical Research</td>
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</tbody>
</table>
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                                 600 Community Drive – 4th Floor  
                                 Manhasset, NY 11030 |
| **Phone**                 | (516) 225-6397 |
| **Email**                 | dgiannis@northwell.edu |

<table>
<thead>
<tr>
<th>Name</th>
<th>Martin Lesser, PhD</th>
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<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Professor and Director of Biostatistics, Institute of Health Innovations &amp; Outcomes Research, Feinstein Institutes for Medical Research</td>
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<td><strong>Address</strong></td>
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<td><strong>Email</strong></td>
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<thead>
<tr>
<th>Name</th>
<th>Cristina Sison, PhD</th>
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<tr>
<td><strong>Title</strong></td>
<td>Assistant Director of Biostatistics, Institute of Health Innovation &amp; Outcomes Research, Feinstein Institutes for Medical Research</td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
</tr>
<tr>
<td>Phone</td>
<td>(516) 465-1950</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:CSison@northwell.edu">CSison@northwell.edu</a></td>
</tr>
</tbody>
</table>
### CPC CONTACTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Victoria Anderson, MPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>DSMB Clinical Operations Manager</td>
</tr>
<tr>
<td>Address</td>
<td>CPC Clinical Research</td>
</tr>
<tr>
<td></td>
<td>13199 E. Montview Blvd. Suite 200</td>
</tr>
<tr>
<td></td>
<td>Aurora, CO 80045</td>
</tr>
<tr>
<td>Phone</td>
<td>(303) 860-9900</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:Victoria.Anderson@cpcmed.org">Victoria.Anderson@cpcmed.org</a></td>
</tr>
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<table>
<thead>
<tr>
<th>Name</th>
<th>Rita Dale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Reporting Biostatistician</td>
</tr>
<tr>
<td>Address</td>
<td>CPC Clinical Research</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Aurora, CO 80045</td>
</tr>
<tr>
<td>Phone</td>
<td>(303) 860-9900</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:Rita.Dale@cpcmed.org">Rita.Dale@cpcmed.org</a></td>
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</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Susie Bachler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>DSMB Coordinator</td>
</tr>
<tr>
<td>Address</td>
<td>CPC Clinical Research</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Phone</td>
<td>(303) 860-9900</td>
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<tr>
<td>Email</td>
<td><a href="mailto:Susie.Bachler@cpcmed.org">Susie.Bachler@cpcmed.org</a></td>
</tr>
<tr>
<td>CHARTER APPROVALS</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
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<tr>
<td><strong>DSMB Chair:</strong></td>
<td></td>
</tr>
<tr>
<td>James Douketis</td>
<td>Date</td>
</tr>
<tr>
<td><strong>DSMB Member:</strong></td>
<td></td>
</tr>
<tr>
<td>Sam Schulman</td>
<td>Date</td>
</tr>
<tr>
<td><strong>DSMB Member:</strong></td>
<td></td>
</tr>
<tr>
<td>John Kittelson</td>
<td>Date</td>
</tr>
</tbody>
</table>
ATTACHMENTS

Flow of Data and Safety Information

The following describes the flow of data to support the safety reviews by the DSMB Chair every 2 weeks throughout the course of the trial. The same flow will be employed for the full safety meetings for the DSMB planned at approximately 25%, 50%, 75% and 100% of enrollment.

- **Study Site**
  - Enters AEs and SAEs, randomization assignment and other clinical data in REDCap Clinical Database in near real time

- **Northwell/Feinstein**
  - Codes AEs and SAEs and transfers all clinical data

- **CPC**
  - Creates Closed Report with subject safety results by treatment group for DSMB Chair every 2 weeks

- **DSMB Chair**
  - Reviews Closed Report with subject safety results by treatment group every 2 weeks
  - Emails recommendation to PI following safety review every 2 weeks
Interim Analysis Plan

STATISTICAL DESIGN

HEP-COVID trial statistical design

Assuming a 40% relative risk reduction in the primary efficacy outcome with LMWH treatment (4) and an incidence of the primary efficacy endpoint of 42% in the usual medical care arm (2, 4, internal Northwell data), 246 patients will be needed to be enrolled (123 in each arm) to have 80% power with a two-sided significance level of 0.05. Assuming a 20% drop out rate, we will need 308 patients in total. The primary analysis will be done in the per-protocol population. The per protocol analysis set will consist of all patients who received at least 80% of planned therapy. There will be a single interim analysis as described below.

HEP-COVID trial interim analysis design

Under the design assumptions with 246 patients, therapeutic dose treatment with LMWH treatment will be deemed to be superior to prophylactic/intermediate dose treatment (i.e., 2-sided p < 0.05) if upon trial completion the risk of a primary efficacy event in the therapeutic LMWH group is -0.117 (11.7%) lower than in the prophylactic/intermediate dose group. With 123 participants a difference of 11.7% corresponds to a difference of 15 events (0.117*123 =~ 15); thus, therapeutic LMWH will be deemed to be superior if there are 15 or more fewer events with therapeutic LMWH when compared to control treatment.

A single interim analysis is planned after the primary outcome status is observed on half (123, or approximately 62 per arm) of the randomized patients. The interim analysis design uses an Emerson-Fleming symmetric design [REF] with O'Brien-Fleming type decision criteria. The analysis will allow early termination for evidence of efficacy if the risk with therapeutic LMWH is -0.234 (23.4%) lower in than the risk with control treatment. Table 1 shows the statistical inference that would be reported if the trial stops at the critical value (15 fewer events) at both the interim and final analyses. Table 2 shows the statistical operating characteristics of the design.

Table 1: Statistical inference upon trial completion.

<table>
<thead>
<tr>
<th></th>
<th>Efficacy Decision</th>
<th>Futility Decision</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>CI (L, U)</td>
</tr>
<tr>
<td>Interim Analysis</td>
<td>0.234</td>
<td>(-0.338, 0.068)</td>
</tr>
<tr>
<td>Final Analysis</td>
<td>-0.117</td>
<td>(-0.234, 0.000)</td>
</tr>
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</table>

For example at the interim analysis, efficacy is decided if the risk is -0.234 (23.4% reduction in risk of the primary efficacy event with therapeutic LWMH. Futility is decided if the risk of an event is larger with therapeutic dosing than with prophylactic dosing. The study continues to the final analysis if the observed risk difference is between -0.234 and 0.000.
At the final analysis superiority is decided (1-sided p<0.025) if the observed risk is smaller than -0.0117. The confidence intervals and p-values show the result that would be reported (e.g., the hypotheses that would be ruled out) if the observed ARR was equal to the decision boundary. For example, if the observed risk difference equals -0.234 at the interim analysis, then the 95% confidence rules out reductions smaller than 33.8% or larger than 6.8% with 1-sided p=0.0027.

Note that a risk difference of -0.234 corresponds to 15 fewer events (0.234*62 =~ 15); thus, the decision criteria in Table 1 mean that an efficacy decision is reached if there are 15 or more fewer events with therapeutic LMWN treatment and futility is decided if there is any excess of events with therapeutic LWMH when compared with control. If the trial is not stopped early then efficacy is decided if the risk difference is smaller than -0.117, which also corresponds to a 15 or more fewer events in the therapeutic dose group.

The statistical properties of the interim analysis design include the power, the average sample size of trials that are monitored using this design, and the probability of stopping at the interim analysis. These properties are a function of the true treatment effect; specifically, ARR = -0.168, ARR = -0.210, and ARR = -0.252 denotes a relative risk of 60%, 50%, and 40% of therapeutic dose relative to prophylactic dose (risk = 0.42); e.g. P1 = 0.252 = 0.42*0.6 so ARR = 0.252 - 0.420 = -0.168.

Table 2: Statistical properties of the interim monitoring design.

<table>
<thead>
<tr>
<th>True treatment effect</th>
<th>Statistical properties of the design</th>
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</thead>
<tbody>
<tr>
<td>P1</td>
<td>Power</td>
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<tr>
<td>0.252</td>
<td>0.804</td>
</tr>
<tr>
<td>0.210</td>
<td>0.941</td>
</tr>
<tr>
<td>0.168</td>
<td>0.988</td>
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</table>

The discrete nature of the outcome measurement means that the above properties a somewhat different from those in Table 2; specifically, the power and type I error rate are both smaller (power = 0.78; type I error = 0.023).
The statistical properties of the interim analysis design include the power the average sample size of trials that are monitored using this design and the probability of stopping at the interim analysis. These properties are a function of the true treatment effect; specifically, \( \text{ARR} = -0.168 \), \( \text{ARR} = -0.210 \), and \( \text{ARR} = -0.252 \) denotes a relative risk of 60%, 50%, and 40% of therapeutic dose relative to prophylactic dose (risk = 0.42); e.g. \( P1 = 0.252 = 0.42 \times 0.6 \) so \( \text{ARR} = 0.252 - 0.420 = -0.168 \).

Reference:
# 14.8 Appendix H

## DataMart Data Elements

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Past Medical History</th>
<th>Active Problems (H&amp;P)</th>
<th>MEDS</th>
<th>History</th>
<th>Vitals/Physical Exam (consider all vitals later)</th>
<th>Labs (consider all labs later)</th>
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<tbody>
<tr>
<td>Patient Name</td>
<td>Heart disease</td>
<td>All active problems</td>
<td>PMH / Meds</td>
<td>International travel (discrete fields: ED</td>
<td>Temp (first, highest, lowest, median, last)</td>
<td>CBC w/diff (all results)</td>
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<td>DOB</td>
<td>Immunocompromised</td>
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<td>ACEI</td>
<td>ADULT Triage Note)</td>
<td>Oxygen saturation (first, lowest, median, last)</td>
<td>LDH</td>
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<td>MIN</td>
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<td>Acute kidney injury measure</td>
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<td>Insulin</td>
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<td>Heart rate (first, highest, lowest, median, last)</td>
<td>(back end Sunrise table <em>Michael Qiu knows</em>)</td>
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<td>Facility</td>
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<td>Prolactin</td>
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<td>Ethnicity</td>
<td>Multiple COVID test results</td>
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<td>Patient home zip code</td>
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<td>CK-MB</td>
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<td>Patient insurance</td>
<td>Echocardiography impression (= EF% discrete?, PMH of CHF vs. new/change)</td>
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<td>ED Resident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>aptt</td>
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<tr>
<td>Team – LU COVID Rule Out (± NSUH version)</td>
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<tr>
<td>Hospital Orders</td>
<td>Imaging (w/ time and date stamps)</td>
<td>Visit / Outcome Info</td>
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<td></td>
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<tr>
<td>----------------</td>
<td>----------------------------------</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Mechanical vent order&lt;br&gt;Vent flowsheet info (all patients have vent flowsheet while some will be missing an order)&lt;br&gt;Transfer to higher level of care (MICU)&lt;br&gt;Vent Data (Tidal Vol/PEEP/FIO2/Mode)&lt;br&gt;Hemodialysis, PD, CRRT&lt;br&gt;Oxygen therapy (nasal cannula, high flow, non-invasive)&lt;br&gt;ECMO</td>
<td>x-ray impression&lt;br&gt;CT chest impression (w and w/o contrast)&lt;br&gt;CTA chest impressions</td>
<td>Length of Stay&lt;br&gt;Current patient vs. discharge&lt;br&gt;Discharge to [Facility/Home]&lt;br&gt;Diagnoses: PNA, ARDS&lt;br&gt;All discharge diagnoses&lt;br&gt;Death&lt;br&gt;Repeat Admission (is this a repeat admission within 30 days?)</td>
<td></td>
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</table>
Introduction: The purpose of this documentation is to provide the investigator and the research team with instructions as to how to randomize subjects into a randomized clinical trial using the Biostatistics Randomization Management System (BRMS).

A. Obtaining a Biostatistics Randomization Management System account and establishing a password:
   1. Submit written IRB approval letter and IRB approved protocol to the statistician assigned to your project.
   2. Statistician, in consultation with PI or designee, will create the randomization plan and establish all of the authorized users.
   3. Login instructions, with an automated password, will be sent via e-mail to all designated (first time) users.
   4. The first time the system is used, it will be necessary for you (the “user”) to reset the automated password to one of your own choice, as per the following instructions:
      a. Copy and paste or type in browser https://fimr.northwell.edu/biostatRMS/ (you might want to bookmark this page for future use.)
      b. Use your email address and automated password (case sensitive) to log into the system. Before proceeding, you will be asked to change your automated password to one of your own choice.
   5. For all future projects, the same login and password should be used. You do not need to repeat this procedure.

B. Password Problems? - Retrieve or Reset your password.
   1. On the login screen, click the "Forgot your password?" link.
   2. Enter your User Name (your email address) and press Submit.
   3. You should immediately receive an email which contains a temporary password.
   4. On the login screen, enter your user name, temporary password, and press Submit.
   5. You should get a prompt that your password had expired and you must change it. Click OK.
   6. Enter your user name, temporary password, new secure password, and click Submit.
   7. You should get a prompt that you successfully changed your password.

C. Log into BRMS
   1. Copy and paste or type in browser https://fimr.northwell.edu/biostatRMS/ or use your bookmarked page.
2. Use your email address and password (case sensitive) to log into the system.
3. When you log in successfully, you should see the System Home Page which will list all of the projects for which you are an authorized user.

D. View the Parameters for a Specific Project
1. On the Home page, click on the "Pad and Magnification Glass" icon to view the Project Summary.
2. You will see pertinent information related to your project, such as PI information, a list of project personnel and roles, list of sites, strata and their levels, and treatment arms.

E. How to Randomize a Subject
1. On the Home page, click on the “Coin Toss” icon to randomize a subject.
2. Select the Site from which the subject is being randomized.
3. If applicable, select the appropriate strata levels for that subject.
4. Enter subject's information (Initials, Unique Subject ID, DOB) and Last Name of Randomizer. (The unique Subject ID is a number/letter combination that is used by the site to identify a subject. It can be a sequential number assigned by the patient’s provider, a medical record number, etc. The use of social security numbers is highly discouraged.)
5. Click the Confirm button and, on the next screen, check that the randomization information for that subject is correct. 
   NOTE: The randomization system is not designed to validate the information entered by the user. Therefore, it is the user’s responsibility to carefully verify that the entered information is correct before proceeding to Step #6.
6. If the information is correct, click the Randomize Subject button. If the information is not correct, click Cancel. You will be brought back to the previous screen to edit the information.
7. You will be brought back to the Home page to receive the randomization # and assignment arm for the subject randomized.
8. You, and all other users who are authorized as email recipients, will also receive an email confirmation of the randomization detailing the transaction. Example of e-mail to be received:

   Subject CC for project ST0001 (IRB#14-345) has been randomized.

   The subject should receive Treatment: Placebo
   Randomization Number: RZ1011121001
   Confirmatory emails sent.

   Project ID: ST0001

   Stratum Combination: Lenox Hill; Age: 50+; Gender: Female
   Subject Initials: CCP

   Patient ID: 575622 Subject

9. Since the Northwell Health e-mail system scans emails for possible PHI, all email accounts outside the Health System may receive an encrypted email with the following message: You have a Northwell Health Secure Email message from biostatwebteam@northwell.edu. To view the secure message, click here. Follow the instructions accordingly to view this email.

F. View Information about Randomized Subjects
1. Click on the "Human" icon. The number to the lower right of the icon represents the number of
subjects randomized thus far. The next screen will list all randomized subjects and selected parameters.
   a. If you are finished looking at the screen, you may close it by clicking the “x” on the top right corner.
   b. If you would like to add a comment, click on the “Notepad” icon for a specific subject. Enter a comment and press the “Save Comment” button. To exit the comment screen, click the “x” on the top right corner.
   c. If you would like to print the screen and/or save it as a PDF, click on the print icon, then follow the usual procedures for saving and/or printing a PDF file.

G. Break the Blind for a Specific Subject (for blinded studies only)
   1. In the event that the blind needs to be broken, first obtain the approval of the site or trial PI.
   2. Click on the “Eye” icon.
   3. Enter information for a subject you wish to "unblind" (i.e. Site, Subject’s Initials, Unique ID, DOB).
   4. Enter the reason for breaking the blind in the text box at the bottom of the screen.
   5. If the information is correct, click the Break the Blind button. If the information is not correct, click Cancel. You will be brought back to the previous screen to edit the information.
   6. You, and all other users who are authorized as email recipients, will receive an email confirmation of the breaking of the blind for that subject.

   NOTE: Breaking the blind in a blinded study is a protocol violation, and is subject to regulatory oversight by the IRB, ORC, DSMB, FDA, and NIH. Even though such violation may be permissible and justifiable as per the protocol, it is important that the reason for breaking the blind is clearly stated. It is generally advisable that, in non-emergency situations, the PI first consult with the project statistician to discuss breaking a blind. The internal audit system will electronically capture information on all users who break the blind.

H. What to do if a Subject was Incorrectly Randomized
   There are typically 3 main reasons a subject may have been incorrectly randomized. The subject:
   • did not meet inclusion/exclusion criteria and this was discovered after randomization.
   • was randomized using the wrong stratum.
   • received the wrong treatment (i.e., was randomized to one treatment but received another).

   If a subject is incorrectly randomized, there are 3 actions you must take:
   1. Contact the trial statistician to get any statistical advice (typically, an ineligible or incorrect randomization is not corrected but is left as is, with appropriate documentation as noted in (2) below).
   2. Add a note in the online randomization system as follows:
      Click on the "Human" icon for the project on the Home page. The next screen will list all randomized subjects. Click on the “Notepad” icon for the specific subject that was incorrectly randomized. Enter a comment that states the reason for incorrect randomization and press the "Save Comment" button. To exit the comment screen, click the “x” on the top right corner.
   3. Contact the IRB to determine if, how, and when the protocol violation should be reported to the IRB.

I. Log Out
   1. Click on Log Out button. You should see: “You successfully logged out of the system”.

   For any questions regarding randomization or any problems logging on to the system, please contact the randomization coordinator in the Biostatistics Unit at 516-465-1950.

END OF DOCUMENTATION
RESEARCH SITE AGREEMENT

This Research Site Agreement ("Agreement"), effective as of the last date of signature below ("Effective Date"), is made by and between The Feinstein Institutes for Medical Research, a New York not-for-profit corporation and 501(c)(3) medical research organization, for itself and on behalf of Northwell Health, Inc., with an address at 350 Community Drive, Manhasset, NY 11030 ("Sponsor") and ___________________________ ("Participating Institution"). Each of Sponsor and Participating Institution is also referred to herein singly as the “Party” and together as the “Parties”.

WHEREAS Sponsor is a not-for-profit medical research organization concerned with the diagnosis, treatment and prevention of disease and clinical research for the improvement of health;

WHEREAS Sponsor has initiated and undertaken a clinical trial entitled Systemic Anticoagulation with Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients (HEP- COVID Trial) (the “Study” or “Clinical Trial”) through its investigator, Alex C. Spyropoulos, MD, FACP, FCCP, FRCPC ("Chief Investigator");

WHEREAS Participating Institution desires to participate in the Clinical Trial and Sponsor desires that Participating Institute participate in the Clinical Trial; and

WHEREAS Participating Institution has the facilities and expertise to conduct the Clinical Trial.

NOW THEREFORE, in consideration of the mutual promises set forth herein, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

1. Definitions

1.1. “Affiliate” means any business entity which controls, is controlled by, or is under the common control with a Party. For the purposes of this definition, a business entity shall be deemed to control another business entity if it owns, directly or indirectly, in excess of 50% of the voting interest in such business entity or the power to direct the management of such business entity.

1.2. “Applicable Law” means all applicable federal, state and local laws, statutes, and regulations pertaining to the conduct of the Clinical Trial and clinical trials and human subjects research generally.

1.3. “Background IP” means any intellectual property, patent, patent application, know-how and trade secret owned by a Party or its Affiliates prior to the Effective Date of this Agreement which is provided to the other Party to use solely in performance of the Clinical Trial.
1.4. “**Clinical Trial Authorization**” means an authorization for the conduct of the Clinical Trial from the relevant Regulatory Authority, obtained in accordance with Applicable Law.

1.5. “**Clinical Trial Subject**” or “**Subject**” means a person recruited to participate in the Clinical Trial.

1.6. “**Confidential Information**” means all information, data and materials concerning the arrangements contemplated by this Agreement or the technical, business or other affairs of one Party or its Affiliates that it discloses to the other Party or the other Party obtains pursuant to or in connection with the Clinical Trial or this Agreement.

1.7. “**Data**” means all work, clinical and other data, and results of experimentation and testing that are recorded in the Clinical Trial database after database freeze.

1.8. “**ICH GCP**” means current practices required by: (a) the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) E6 and E11; and (b) provisions of Title 21 of the Code of Federal Regulations (including without limitation Parts 11, 50, 54, 56, 312, 314, 320, 601 and 610) and all rules, regulations, order and guidance’s published thereunder.

1.9. “**Intellectual Property**” means any invention or discovery conceived in performance of the Clinical Trial.

1.10. “**Protocol**” means the description of the Clinical Trial referenced in and incorporated by reference herein at Exhibit A and all amendments thereto.

1.11. “**Regulatory Authority**” includes but is not limited to the U.S. Food and Drug Administration, and other applicable regulatory authorities.

1.12. “**Results**” means the results of the Clinical Trial including, without limitation, all Data and any reports generated thereto under this Agreement.

1.13. “**Trial Site**” means the premises used by Participating Institution in which the Clinical Trial will be conducted by Participating Institution.

2. **Scope of Work**

2.1. Participating Institution shall conduct and supervise the Clinical Trial at the Trial Site through its investigator, [ ], who is an employee of Participating Institution (“**Site Investigator**”). Participating Institution shall notify Sponsor promptly if Site Investigator is unable or unwilling to continue the Clinical Trial or if Site Investigator’s affiliation with Participating Institution ceases in which case Participating Institution shall use its reasonable efforts to find a replacement investigator who is mutually agreeable to both Sponsor and Participating Institution. If no mutually agreeable replacement investigator can be found, Sponsor may terminate this Agreement.

2.2. Participating Institution represents that Site Investigator has the necessary registration and has the expertise, time and resources to perform the Clinical Trial and that Site Investigator meets and will continue to meet the conditions set out at **Article 3** to this Agreement.

2.3. Participating Institute shall and shall require Site Investigator (i) to conduct the Clinical Trial in
accordance and compliance with (a) all Applicable Law as well as all relevant guidance relating to medicines and clinical trials including, but not limited to, ICH GCP and the World Medical Association Declaration of Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”, (b) the Protocol, (c) the terms of this Agreement, and (d) the terms and conditions of the approval of the relevant research ethics committee(s) or institutional review board(s) (hereinafter the “IRB”); and (ii) to coordinate, cooperate and collaborate with Sponsor and Sponsor’s agents and contractors.

2.4. Participating Institution shall supervise Site Investigator and those Study Staff employed by Participating Institution, and Participating Institution shall ensure that all Study Staff are appropriately trained, qualified, certified, and informed of and abide by the applicable terms of this Agreement.

2.5. Sponsor may amend the Protocol at any time. Any such amendment shall be in writing and sent to Participating Institution, and will not take effect until approved by the IRB.

2.6. Should there be any inconsistency between the Protocol and the terms of this Agreement, the terms of the Protocol shall prevail with regards to scientific matters and this Agreement shall prevail with respect to contractual matters.

2.7. Participating Institution shall ensure that any clinical samples required to be tested by or at Participating Institution in relation to this Clinical Trial are tested in accordance with the Protocol.

2.8. Participating Institution shall be responsible for procuring and maintaining at its own cost and expense all product, including heparin, needed to conduct the Clinical Trial in accordance with the Protocol.

3. Conditions Applicable to Site Investigator and Conflict of Interest

3.1. Site Investigator is free to participate in the Clinical Trial and there are no rights which may be exercised by or obligations owed to any third party which might prevent or restrict Site Investigator’s performance of the obligations detailed in this Agreement. Neither Participating Institution nor Site Investigator is a party to any agreement which might prevent or restrict its, his or her performance of the obligations detailed in this Agreement.

3.2. Neither Site Investigator nor any member of the Study Staff is debarred or disqualified from participating in clinical research by any Regulatory Authority. In addition, Site Investigator is not involved in any regulatory or misconduct litigation or investigation by any Regulatory Authority. No data produced by Site Investigator in any previous clinical study has been rejected because of concerns as to accuracy or because the data were generated by fraud.

3.3. Site Investigator carries medical liability insurance (or Participating Institution carries medical liability insurance covering Site Investigator) or its self-funded equivalent and details and evidence of the coverage will be provided to Sponsor upon request.

3.4. Site Investigator has adequate facilities at Participating Institution’s site (including Trial Site) to perform the Clinical Trial, and Site Investigator is supported and will continue to be supported, by medical and other staff in sufficient number and experience to enable Site Investigator and Participating Institution to perform the Clinical Trial efficiently and in accordance with the Protocol and this Agreement.

3.5. During the Clinical Trial, Site Investigator will not serve as an investigator or other significant participant in any clinical study for another sponsor if such activity might adversely affect his/her ability to
perform Site Investigator’s obligations under this Agreement.

4. Consent and Approvals

4.1. Participating Institution is responsible for obtaining and maintaining any and all Clinical Trial Authorizations and all approvals from the relevant IRB for the conduct of the Clinical Trial at Trial Site. Without limiting the foregoing, Participating Institution shall seek approval of the Clinical Trial, the Protocol, and a written form of informed consent mutually acceptable to Sponsor and Participating Institution from the appropriate IRB. Participating Institution shall keep Sponsor fully apprised of the progress of licensing authority and IRB submissions and shall submit to Sponsor a copy of any Clinical Trial Authorization and IRB approval (e.g., annual IRB approval and re-approval letters and confirmation of IRB approved amendments and consent forms).

4.2. Prior to enrolling a prospective Clinical Trial Subject, Participating Institution shall obtain from each such individual a valid informed consent and HIPAA authorization signed by the individual or such individual’s legally authorized representative. Participating Institution shall conduct the Clinical Trial in a manner consistent with the informed consent and all other applicable consents, including the HIPAA authorization. Such informed consent and HIPAA authorization shall permit Participating Institution and Site Investigator to use and disclose Subject information in accordance with the Protocol for purposes of the Clinical Trial including disclosure to Sponsor and Chief Investigator.

5. Data, Reporting and Monitoring

5.1. Clinical Trial Data and Results

5.1.1. Participating Institution shall keep and maintain, diligently and in sufficient detail to satisfy all applicable legal requirements, such Data and records as are required by this Agreement, the Protocol, and Applicable Law.

5.1.2. Participating Institution shall provide to Sponsor the Clinical Trial documents containing the Data specified in the Protocol and shall prepare same in the manner specified in the Protocol, at the intervals indicated in the Protocol or as otherwise agreed to in writing by the Parties. Sponsor shall own all Data.

5.1.3. Participating Institution shall retain the Clinical Trial documentation in a secure location in accordance with Applicable Law. At Sponsor’s request and reasonable expense, Participating Institution shall retain the Clinical Trial documentation for up to three (3) years beyond the period required to be held by Participating Site according to Applicable Law. After the required retention period has expired, Participating Institution shall provide Sponsor sixty (60) days’ written notice before destroying any Clinical Trial documentation.

5.2. Monitoring and Investigations

5.2.1. If Sponsor reasonably believes there has been any research misconduct in relation to the Clinical Trial at the Trial Site, Sponsor and Site Investigator shall conduct a thorough investigation into any alleged research misconduct.

5.2.2. Participating Institution shall make available to Sponsor (or its agent) the Trial Site, the
Study Staff, and all Clinical Trial documents for purposes of review and audit at mutually agreeable times during regular business hours. If Site Investigator fails to correct any violations of the Protocol, this Agreement, or Applicable Law found in such audit within thirty (30) days after receiving written notice of the violations found during such audit thereof from Sponsor or its agent, Sponsor may immediately terminate this Agreement; provided, however, if the violation would result in imminent harm to a Subject then Sponsor’s immediate termination of this Agreement is not conditioned on such thirty (30) day cure period.

5.2.3. Sponsor and/or Sponsor’s agents or contractors may access the Clinical Trial documents at the Trial Site during mutually agreeable times during normal business hours. Sponsor or Sponsor’s agent or contractor, as applicable, shall comply with Applicable Law regarding the confidentiality of Subjects’ medical records and other health information, shall hold the Subjects’ personal identifying information in confidence, and shall act in accordance with the informed consent and the HIPAA authorization. Subject to the foregoing, Sponsor or Sponsor’s agent or contractor acting on Sponsor’s behalf may copy Participating Institution’s records containing such information to the extent permitted by Applicable Law and the express authorization of the informed consent and HIPAA authorization from relevant Subjects and shall not attempt to contact any Subject except to the extent expressly permitted by the IRB or as required to comply with Applicable Law.

5.2.4. Participating Institution shall provide Sponsor prompt, advance notification of any audit by a Regulatory Authority, which audit is directly related to the Clinical Trial (“Audit”) (or, when advance notification is impracticable, prompt notification of any completed Audit). Participating Institution shall, to the extent not prohibited by Applicable Law, permit Sponsor to review and comment on any written communication from Participating Institution to a Regulatory Authority in connection with such an Audit prior to Participating Institution responding to such Audit, if time permitting. Participating Institution shall promptly provide Sponsor with copies of all communications between Participating Institution and the Regulatory Authority related to such Audit unless prohibited from doing so by Applicable Law. Participating Institution shall promptly take action to correct any undisputed deficiencies found by the Regulatory Authority during the Audit. With respect to a pending audit directly related to the Clinical Trial by the FDA, Participating Institution shall permit Sponsor’s representatives to be present at such audit unless prohibited from so doing by Applicable Law. With respect to any audit by any Regulatory Authority which audit is not directly related to the Clinical Trial, Participating Institution shall promptly notify Sponsor of any final findings of such an audit that would be likely to have an adverse effect on Participating Institution’s ability to conduct the Clinical Trial.

5.2.5. Sponsor shall promptly notify Participating Institution of findings obtained during on-site monitoring activities from the Trial Site, or from Results as obtained as part of the Clinical Trial that could affect the safety of Subjects or their willingness to continue participation, influence the conduct of the Clinical Trial or alter the IRB’s approval to continue the Clinical Trial.

5.3. Reporting and Safety

5.3.1. Unless otherwise specified in the Protocol, Participating Institute through its Site Investigator shall at monthly intervals provide Sponsor with a report detailing the progress of the Clinical Trial at Trial Site including Clinical Trial Subject recruitment. In addition, the Parties may meet at periodic intervals at such normal business times either at Participating Institute location or Sponsor’s location or teleconferences, as the Parties may mutually agree. At these meetings, Site Investigator shall update Sponsor and Chief Investigator on the progress of the Clinical Trial.
5.3.2. Participating Institution shall comply, and shall require that Site Investigator complies with all safety reporting regulations as set forth in Applicable Law. Participating Institution shall immediately send to Sponsor a copy of any correspondence to or from the FDA and/or other Regulatory Authority regarding adverse events or other safety issues directly related to this Trial.

5.3.3. Nothing in this Agreement shall remove or restrict any obligation on either Party to report clinical safety information arising during the Clinical Trial to (i) the Regulatory Authorities where the Clinical Trial is being conducted, in accordance with the local requirements, or (ii) comply with any legal obligations in connection with this Clinical Trial.

6. Indemnity

6.1. Participating Institution agrees to indemnify, hold harmless and defend Sponsor and Chief Investigator and their respective employees, affiliates, agents, trustees, officers and directors, including the IRB ("Sponsor Indemnitees") from and against all any damages, losses, expenses, claims, actions or proceedings brought by a third party (collectively, "Claims"), to the extent directly resulting from or arising out of any (i) the negligence, recklessness or willful misconduct on the part of Participating Institution, its directors, officers, employees and agents (including Site Investigator and Study Staff), in connection with the performance of the Clinical Trial; (ii) a material breach of this Agreement by Participating Institution (including Site Investigator and Study Staff); or (iii) the misuse, disclosure or publication by Participating Institution of Protected Health Information (as defined under HIPAA), or Results other than as permitted by this Agreement and Applicable Law; provided, however, that Participating Institution shall not be liable to the extent a Claim arose due to a Sponsor Indemnitee’s negligence, intentional wrongdoing, or its failure to comply with this Agreement or Applicable Law.

Upon receipt of a notice of Claim arising out of this Agreement, Sponsor will notify Participating Institution promptly, including a copy thereof, served upon it, and shall cooperate fully with Participating Institution and its legal representatives in the investigation of any such Claim, at Participating Institution’s expense. Participating Institution shall have the right to exercise sole control over the defense and settlement of any such Claim, including the sole right to select defense counsel and to direct the defense or settlement of any such Claim; provided that Participating Institution shall not enter into any non-monetary settlement or admit fault or liability on Sponsor’s behalf without the prior written consent of Sponsor, which consent shall not be unreasonably withheld or delayed. Sponsor shall have the right to select and to obtain representation by separate legal counsel and if Sponsor exercises such right, all costs and expenses incurred by Sponsor for such separate legal counsel shall be borne by the indemnified party.

6.2. Sponsor agrees to be responsible for its acts and those of Chief Investigator in conducting the Study limited solely and exclusively to the extent determined to be caused by the gross negligence or willful malfeasance on the part of Sponsor or Chief Investigator.

6.3. Participating Institution shall be relieved of any indemnification obligation hereunder if any Sponsor Indemnitee (i) compromises or settles any Claim without Participating Institution’s prior written approval; or (ii) makes any admission or takes any other action with respect to any such Claim that, in Participating Institution’s reasonable judgment, is prejudicial to the defense of such Claim, without Participating Institution’s prior written approval.

7. Insurance
7.1. **Participating Institution**

7.1.1. During the term of this Agreement, and following termination or expiration of the Study, to cover any claims arising from the Study, Participating Institution shall maintain carrier-issued insurance and/or self-insurance coverages in the following types and amounts indicated below:

- Commercial General Liability insurance with limits not less than $1,000,000 per occurrence and $3,000,000 annual aggregate;
- Professional Liability insurance with limits not less than $1,000,000 per occurrence and $3,000,000 annual aggregate;
- Clinical Trials Liability insurance with limits not less than $5,000,000 per occurrence and $5,000,000 annual aggregate;
- Excess liability insurance with limits not less than $5,000,000 per occurrence and $5,000,000 annual aggregate;
- Network security/cyber/data breach insurance with limits not less than $1,000,000 per claim and $3,000,000 annual aggregate; and
- Statutory workers’ compensation and employer’s liability.

7.1.2. To the extent the insurance is not self-insurance, Participating Institution’s insurance carrier shall have a minimum A.M. Best rating of A/IX, and Participating Institution agrees to provide to Sponsor thirty (30) days’ notice for cancellation or non-renewal of carrier-issued coverage. Further, in the event that any of the above carrier-issued policies are on a claims made basis, (i) such insurance shall be effective as of the effective date of this Agreement and shall continue for a period of three (3) years following term of this Agreement or Participating Institution shall obtain an extended reporting (tail) coverage for the remainder of the three (3) year period; and (ii) Participating Institution shall ensure that tail coverage is purchased in the event of cancellation, termination, or non-renewal to cover any claims arising out of this Agreement.

7.1.3. Prior to the commencement of the Study, Participating Institution shall ensure that a certificate of insurance evidencing the requirements herein is delivered to Sponsor. The minimum amounts of insurance coverage required in this **Section 7.1** shall not be construed to limit Participating Institution’s liability in any way.

7.1.4. Each of The Feinstein Institute for Medical Research and Northwell Healthcare, Inc. and their respective parents, subsidiaries, majority-owned affiliates, directors, officers, trustees, employees, agents and representatives shall be added as additional insured on Participating Institution’s liability policies, which shall be primary and non-contributory to any policy carried by Sponsor.

7.1.5. Sponsor reserves the right to terminate this Agreement in the event that Participating Institution cancels or does not renew its insurance coverage that is required herein.

7.2. **Sponsor**

7.2.1. Sponsor represents that it has, and will maintain during the term of the Study and for at
least three (3) years thereafter for claims-made coverage general liability insurance through a program of
insurance or self-insurance and professional liability insurance each with limits of not less than $1,000,000
per occurrence and $3,000,000 in the aggregate. Further, Sponsor represents that it has, and will maintain
during the term of the Study, statutory workers’ compensation and employer’s liability insurance. Sponsor
will provide a certificate of insurance as evidence of such insurance coverage to Participating Institution
upon request.

8. Confidentiality; Communication of Data

8.1. In furtherance of the conduct of the Clinical Trial, it may be necessary or desirable for
Sponsor to disclose proprietary and/or other confidential information ("Confidential Information") to
Participating Institution and Site Investigator. All Confidential Information disclosed by Sponsor under this
Agreement or otherwise in connection with the Clinical Trial shall remain the property of Sponsor and
Participating Institution shall, and shall ensure that Site Investigator and Study Staff shall use and disclose
such Confidential Information only in connection with the legitimate purposes of this Agreement and then
only to those who have a need to know it and are obligated to keep same in confidence. Participating
Institution agrees further to ensure that such Information shall be safeguarded with reasonable care.
Participating Institution and Site Investigator shall treat each item of Confidential Information as
confidential during the term of this Agreement and for a period of seven (7) years thereafter.

8.2. The foregoing confidentiality obligation shall not apply when, after and to the extent the
Confidential Information disclosed: (i) is published or is now, or hereafter becomes generally available to
the public other than as a result of a breach of the undertakings hereunder by the receiving Party or its
Affiliates; (ii) was already in the possession of Participating Institution without restriction as to
confidentiality at the time of disclosure as evidenced by competent written records, or (iii) is subsequently
received by Participating Institution from a third party without restriction and without breaching
anyconfidential obligation between the third party and Sponsor.

8.3. If Participating Institution and Site Investigator are required by law, regulation, order,
decree, subpoena, or other legal process, to disclose Confidential Information, Participating Institution and
Site Investigator shall give Sponsor prior written notice to permit Sponsor an opportunity to seek a
protective order or other appropriate protection with respect to such Confidential Information.

8.4. The Parties agree to adhere to the principles of and applicable laws governing medical
confidentiality in relation to Clinical Trial Subjects involved in the Clinical Trial. Without limiting the
foregoing, Participating Institution shall not, and shall ensure that Site Investigator and Study Staff shall
not, disclose to Sponsor Protected Health Information ("PHI") as defined in 45 CFR part 164, orindividually
identifiable health information as defined in 45 CFR part 142 concerning a Subject, unless required to
report adverse event findings in accordance with Applicable Law or authorized pursuant to theinformed
consent and HIPAA authorization. Identities of Subjects will not be disclosed to third parties without prior
written consent of the Subject, except in accordance with the requirements of all Applicable Laws relating
to data protection. Each Party agrees not to use or further disclose any PHI or individually identifiable
health information concerning a Subject other than as permitted by this Agreement and the requirements
of the federal privacy regulations contained in 45 CFR part 142. If in connection with the Clinical Trial a
Party and/or any of its affiliates, agents, servants and employees come into contact with individually
identifiable health information relating to patients of the other Party who are not Subjects, bothParties and
their affiliates, agents, servants and employees agree to maintain the confidentiality of such information
and not use it for any purpose.
9. Intellectual Property

9.1. The Party who owns the Background IP shall continue to have sole ownership of the Background IP and no license, grant or assignment, expressed or implied, by estoppels or otherwise, with regard thereto is intended by, or shall be inferred from the non-owning Party’s use of the Background IP in performance of the Clinical Trial.

9.2. As between Sponsor and Participating Institution (including Site Investigator), Intellectual Property, whether or not patentable, which arise from the Study or involve the use of Confidential Information or Results or the use of the Protocol shall be the sole property of Sponsor (“Sponsor Inventions”). The rights of Sponsor with respect to Sponsor Inventions will not be limited by any dispute between Sponsor and Participating Institution regarding this Agreement or otherwise.

10. Publicity and Publication

10.1. No Party to this Agreement will use the name or logos of the other Party or any member of a Party’s staff including employees and medical staff members, in any publicity, advertising, promotional literature, news release or any other publicity matter without the prior written approval of an authorized representative of the other Party, unless specifically authorized in this Agreement. Notwithstanding the foregoing, this Section 10.1 shall not restrict any Party’s ability to use the other Party’s name in regulatory filings, prosecuting or defending litigation, and complying with applicable governmental regulations and legal requirements and either Party may use the other Party’s name for internal reports generated in the normal course of business, or acknowledgement of sponsorship as required by law or the guidelines of a scientific or academic organization.

10.2. Upon completion of the Clinical Trial, Sponsor shall prepare the Results for publication and such publication shall include Results generated by Participating Institution and Site Investigator and acknowledge the Participating Institution and Site Investigator’s contribution.

10.3. In addition, Participating Institution acknowledges that Sponsor has agreed to make public a summary of the Protocol and a summary of the Results by posting such information on www.ClinicalTrials.gov and Participating Institution agrees that such disclosure may include only the name of Participating Institution and Site Investigator, among others involved in the Clinical Trial.

11. Payments. There shall be no fees, charges or other payments made or payable by Sponsor to Participating Institution for conducting this Trial or otherwise in connection with the Clinical Trial. Participating Institution shall be responsible for funding its own activities, including those of Site Investigator, in the conduct of the Clinical Trial.

12. Term and Termination

12.1. This Agreement is effective as of the Effective Date and will remain in effect until the earlier of (i) database freeze; or (ii) earlier termination of the Clinical Trial in accordance with the terms of this Section 12.1.

12.1.1. Either Party may terminate this Agreement (i) immediately to protect the health and safety of Subjects involved in the Clinical Trial; or (ii) upon thirty (30) days’ prior written notice if the other
Party is in material breach of its obligations hereunder and fails to cure such breach within thirty (30) days of a written notice from the injured Party specifying the breach.

12.1.2. In addition to the foregoing, Sponsor may terminate this Agreement by providing Participating Institution with thirty (30) days’ prior written notice (i) for any or no reason; (ii) if Site Investigator is no longer able to act as Site Investigator and no replacement mutually agreeable to Sponsor and Participating Institution can be found; or (iii) if Participating Institution is insolvent or if an order is made or a resolution is passed for its winding up (except voluntarily for the purpose of solvent amalgamation or reconstruction) or if an administrator, administrative receiver or receiver is appointed over the whole or any part of its assets, or if it makes any arrangement with its creditors.

12.2. At close-out of the Clinical Trial Site following termination or expiration of this Agreement each Party shall promptly at the election and reasonable expense of the other Party deliver to such other Party or destroy any or all of the other Party’s Confidential Information and any other unused materials provided to that other Party pursuant to this Agreement. Participating Institution shall be entitled to retain a copy of any Confidential Information for record retention purposes and to provide the appropriate medical care to former and present Clinical Trial Subjects. In addition, in no event shall a Party be obligated to return or destroy any Confidential Information in its electronic systems, but shall agree to maintain as Confidential Information under this Agreement.

12.3. Termination of this Agreement will be without prejudice to the accrued rights and liabilities of the Parties under this Agreement provided that, upon termination of this Agreement, Sponsor shall have no obligation to make any payment linked to a milestone not achieved prior to termination.

12.4. If this Agreement is terminated before completion of the Clinical Trial, Participating Institution shall cease enrolling Clinical Trial Subjects immediately, and shall cease conducting the procedures set out in the Protocol to the extent that doing so is medically permissible and appropriate. Participating Institution acknowledges that in the event of such termination, Sponsor shall negotiate in good faith on the subsequent treatment or transfer of the Clinical Trial Subjects and Participating Institution agrees to cooperate and comply with such treatment and/or transfer plan as reasonable.

13. **Relationship between the Parties.** In performing activities under this Agreement, Participating Institution (including Site Investigator and Study Staff) are independent contractors to Sponsor, and do not have the authority to act as an agent or employee of Sponsor. The relationship between the Parties does not constitute a partnership, joint venture, or agency and neither Party shall have the authority to bind the other Party without that other Party’s express, written permission.

14. **Agreement and Modification.** Any change in the terms of this Agreement shall be valid only if the change is made in writing, agreed to, and signed by both Parties. Each term of this Agreement shall be valid and enforceable to the fullest extent permitted by Applicable Law, and if any term or provision of this Agreement or the application thereof to any person or under any circumstance, shall to any extent be invalid or unenforceable: (i) the Parties shall negotiate in good faith so that such term or provision shall be modified in such a way that it becomes valid and enforceable provided such modification must adhere as strictly as possible to the Parties’ original purposes and be given such interpretation as to achieve the Intent of this Agreement; and (ii) the remainder of this Agreement, or the application of such terms to the persons or under circumstances other than those as to which it is invalid or unenforceable, shall not be affected thereby.

15. **Notices.** Any notices given under this Agreement shall be in writing. Notice shall be deemed given
(i) on the date received when delivered personally; (ii) on the date received if delivered by courier; or (iii) five (5) days after the date postmarked if sent by certified or registered mail, return receipt requested, postage prepaid.

**Notices to Sponsor shall be addressed to:**

The Feinstein Institutes for Medical Research  
350 Community Drive  
Lake Success, NY 11042  
Attn: Diane Quinn  

**With a copy to:**  
Northwell Health, Inc.  
Office of Legal Affairs  
2000 Marcus Avenue  
New Hyde Park, NY 11042

**Notices to Participating Institution shall be addressed to:**

With copy to:

Attention: ____________________________

16. **Force Majeure.** Neither Party shall be liable to the other Party or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, epidemic or pandemic, accident, fire, wind, flood or because of any act of God or other cause beyond the reasonable control of the Party affected and the Party affected by such circumstances shall promptly notify the other Party in writing when such circumstances cause a delay or failure in performance. In the event such a delay lasts for four (4) weeks or more either Party shall have the right to terminate this Agreement immediately by notice in writing to the other Party.

17. **Waiver.** No failure, delay, relaxation or indulgence by any Party in exercising any right conferred on such Party by this Agreement shall operate as a waiver of such right, nor shall any single or partial exercise of any such right nor any single failure to do so, preclude any other for future exercise of it, or the exercise of any other right under this Agreement.

18. **Governing Law; Dispute Resolution.** This Agreement shall be governed and construed in accordance with the laws of the State of New York without giving regard to its conflict of law policies. The Parties shall use their reasonable efforts to resolve any dispute arising out of or in connection with any provision of this Agreement in good faith.

19. **Third Party Rights; Assignment.** Except for the rights expressly granted hereunder, nothing in this Agreement shall be construed as conferring upon a Party or any other third party any other or additional rights hereunder including in or to confidential information, intellectual property, or inventions of third parties. Participating Institution may not assign this Agreement without the prior written approval of Sponsor. Participating Institution shall not subcontract any of its obligations hereunder without prior written approval from Sponsor.

20. **Headings; Counterparts.** The Section and Article headings in this Agreement are for reference
only, and shall not affect the interpretation or meaning of any provision of this Agreement. This Agreement shall be executed in one or more counterparts, each of which when executed and delivered will be deemed an original, but all of which when taken together will constitute one and the same agreement. A signed copy of this Agreement delivered by facsimile, e-mail, or other means of electronic transmission is deemed to have the same legal effect as delivery of an original signed copy of this Agreement.

[Remainder of page intentionally blank; signatures follow]

The Feinstein Institutes for Medical Research on behalf of Northwell Health, Inc.

________________________________________
Name: Diane C. Quinn
Title: AVP, Finance
Date: __________________________

[Participating Institution]

________________________________________
Name: __________________________
Title: __________________________
Date: __________________________

Read and understood

________________________________________
Name: Alex C. Spyropoulos, MD
Title: Chief Investigator
Date: __________________________

Read and understood

________________________________________
Name: __________________________
Title: Site Investigator
Date: __________________________
Exhibit A

Protocol

Incorporated by reference
GENERAL STATEMENT of PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the investigational drug service in the Department of Pharmacy.

SCOPE

This policy applies to all members of Long Island Jewish Medical Center workforce including, but not limited to employees, medical staff, volunteers, students, physician office staff, and other persons performing work for or at Long Island Jewish Medical Center.

RESPONSIBILITIES

1. The Principal Investigator (PI) and the Delegated Research Staff

a) Study Feasibility:

The PI and the delegated research staff are responsible for notifying the Department of Pharmacy of any potential studies and for providing any necessary documents to secure resources and establish procedures.

b) Study Initiation, Conduct and Closure:

The PI and the delegated research staff are responsible for:

- Notifying the Department of Pharmacy of any changes in study status, which include but not limited to approval, renewal, amendments, completion, closure and termination,
- Providing 1) IRB approval and renewal letters, 2) initial and updated lists of authorized prescribers, 3) essential documents and their updated versions and 4) any pertinent communications from the sponsors throughout the study,
- Notifying the pharmacist(s) of upcoming dosing schedules and any changes in subject status using email and of upcoming monitoring visits,
- Providing the following documents for dose preparations in advance, if possible.
  - *The first and signature page of the signed informed consent form* for each
subject PRIOR to the first dispensation.
- Prescriptions and drug orders signed ONLY by the authorized prescribers for each study.
- Any protocol-specific documents for each dispensation (e.g., randomization to treatment arm, dose assignment, assigned kit, bottle or vial numbers and subject weight or BSA) upon availability.

2. The Department of Pharmacy
   a) The delegated pharmacist(s) must comply with all applicable federal and state statutes, rules and regulations and Health System policies on the management of investigational drugs (including procurement, storage, preparation, dispensation, disposal, accountability, documentation and reporting and record keeping requirements).
   b) The delegated pharmacist(s) must complete any trainings required by the sponsors, the Health System and other applicable organizations.

PROCEDURES

1. Study Feasibility
   a) The PI and delegated staff will contact the main research pharmacist to discuss any necessary resources and procedures for each study.
   b) The delegated pharmacist(s) will request the following documents and information:
      o Study protocol
      o Investigator’s brochure
      o Pharmacy manual
      o Drug procurement plan and (if the pharmacy department procures the product) reimbursement procedures
   c) The delegated pharmacist(s) will assess study feasibility and plan for procurement, storage, preparation, dispensation, disposal, accountability and documentation of the investigational drug.
   d) If necessary, procure and secure any equipment and ancillary supplies.
   e) If necessary, establish a contract with the PI.
   f) The delegated pharmacist(s) may need to meet with potential sponsors during site-selection visits. They should prepare a list of any pertinent questions and answers to frequently-asked-questions (or present this SOP).

2. Study Initiation
   a) Upon the notification of the IRB approval, the delegated pharmacist(s) will establish a protocol-specific investigational drug (or pharmacy) binder containing:
      o IRB approval letter
      o Approved protocol
      o Investigator’s brochure
      o Pharmacy manual
      o List of authorized prescribers
      o Randomization charts (if necessary)
      o Any protocol-specific forms (e.g., investigational drug order form, drug
accountability record form, shipping records)
- For sponsor initiated studies, access to IWRS for online study documents
  b) The delegated pharmacist(s) may need to meet with the sponsors during site-initiation visits. They should prepare a list of any pertinent questions.
  c) The delegated pharmacist(s) will complete any required trainings and procedures (e.g., IVRS/IWRS, dose preparations) and retain documentation.
  d) The delegated pharmacist(s) will discuss the drug procurement plan with the research team.

3. Drug Procurement
   a) The delegated pharmacist/nurse will order investigational drugs according to the sponsor’s instructions.
   b) The delegated pharmacist/nurse will retain both blank and completed drug order forms for their records.

4. Receipt of Drug
   a) Upon receipt of a drug package, the delegated pharmacist(s) will verify the following information in the shipping document and confirm the receipt as instructed by the sponsor.
      o Protocol, sponsor and PI information
      o Subject information (for subject-specific investigational drug supply)
      o Drug name, dosage form and strength
      o Package size and quantity
      o Lot or batch number
      o Kit, bottle or vial numbers
      o Expiration or retest date
      o Temperature during transit
      o Damage and discrepancy
   b) The delegated pharmacist(s) will retain the shipping documents and delivery/receipt confirmation in the investigational drug binder. Pharmacist to confirm shipment via IWRS if applicable.

5. Drug Storage
   a) The delegated pharmacist(s) will ensure the following storage conditions:
      o Security and safety
        Research medications are stored in designated locations according to temperature requirements as per protocol. Access to investigational drugs is limited to authorized personnel only.
        - Dedicated storage shelf, cabinet, refrigerator and freezer space is separate from non-research drugs, other supplies and food.
        - Storage compartments are labeled with protocol and drug information.
        - Each drug, dosage form and strength under the same study is stored in separate compartments.
        - Used, returned and expired drugs are separated from the working stock.
        - Safeguards such as caution labels for the same drugs used in multiple protocols
Drug storage temperatures
- Refrigerator/freezer temperature as well as room temperature is monitored and recorded at least once a day or as per study protocol.
- When a temperature deviation has occurred, repeat temperature check within 60 minutes. If after 60 minutes temperature is still out of range, contact Department of Engineering/Biomed. Pharmacy management, sponsor, PI and clinical research associate will be notified of temperature excursion as soon as possible. A note to file will be created for affected research medications.
- In the event that a refrigerator malfunctions, medication will be stored in an alternate refrigerator. Refrigerators/freezers are connected to the back-up generator in the event of a black-out situation.

6. Drug Preparation and Dispensation
   a) The delegated pharmacist(s) will verify information in the documents provided by the research team against each protocol, signed informed consent form (the 1st dispensation only) and list of authorized prescribers. These documents will be placed in the investigational study binder. Clarify any questions with the research team in writing. Errors need to be corrected PRIOR to dose preparation.
   b) The delegated pharmacist(s) will complete and retain any protocol-specific documents for each preparation and dispensation.
   c) The delegated pharmacist(s) will follow protocol-specific instructions, site policies, procedures and any applicable regulations for preparation (including compounding and repackaging) and dispensation.
   d) Drug label should retain the following information:
      o "Caution: New drug-limited by federal law (or US) to investigational use"
      o Study identifier (e.g., protocol number)
      o Prescription or drug order number
      o Subject name or initials
      o Subject address or location in facility
      o Subject study identification number
      o Investigational drug name / placebo
      o Investigational drug dosage form and strength
      o Dispensing quantity
      o Administration instructions including dose
      o Directions for storage and other relevant information
      o Preparation or dispensing date and time
      o Expiration date and time
      o Name of prescribing investigator
      o Name or initials of pharmacist
      o Pharmacy name, address and phone numbers
   e) Drug pick-up and delivery
      The research team picks up investigational medication from the Pharmacy or the research pharmacy team delivers medication to the unit.
7. **Drug Disposal**
   a) The delegated pharmacist(s) will obtain and retain written procedures and approval for used, unused and expired investigational drugs PRIOR to their return to the sponsor or on-site disposal.
   b) Upon the termination, discontinuation, recall or completion of investigational study all products must be accounted for. All records of inventory must be kept up to date. All used, unused or expired investigational product (IP) must be appropriately and safely disposed of or returned.
   c) For any Used or Expired products - According to the Investigational study protocol, if sponsor has designated IP is to be returned to their facility follow the drug return methods described in study protocol. If Hospital facility has been designated by sponsor to dispose of IP, then follow Northwell Health’s guidelines for Biomedical, Hazardous and general waste drug disposal.
   d) For any Unused Products- All IP should be returned to sponsor if it is part of their protocol. If the sponsors do not want the unused IP returned to their facility, then the medications would be disposed of as per Northwell Health’s policies: “GR049-Medications and Investigational New Drugs Used in Clinical Research” and “GR050-Use of Controlled Substances in Research”, or as specified in the study protocol.
   e) The delegated pharmacist(s) will record the final disposition in drug accountability records and retain any other disposal records.

8. **Drug Accountability**
   a) The delegated pharmacist(s) will record every drug transaction, including but not limited to, the receipt, preparation, dispensation, transfer, distribution, disposal, scheduled inventory verification, in a protocol-specific drug accountability record form. Complete all information as required in each drug accountability record form.
   b) The delegated pharmacist(s) will use separate drug accountability record sheet for each protocol, drug, dosage form, drug strength, lot number and storage location.
   c) The delegated pharmacist(s) will schedule periodic inventory verification at least monthly to reconcile any discrepancies, secure sufficient supplies for upcoming subject visits and dispose of any expired drugs.

9. **Special Situations**
   a) Mailing or transporting investigational drugs is in accordance with sponsor’s guidelines.
   b) Re-labeling investigational products upon request from the sponsors as per instructions from the sponsors.
   c) Subjects participating in clinical research at another institution:
      o The admitting physician or the investigator is responsible for notifying the Department of Pharmacy immediately, obtaining the protocol, IRB approval, signed consent form and other relevant documents from another institution and providing their copies to the Department of Pharmacy.
      o The Department of Pharmacy will be responsible for the management of the investigational drug pursuant to the physician’s order and protocol.
   d) **Procedure for individual patients in emergency settings** (Expanded access emergency use; also known as compassionate use)
The investigator will provide the following documents:

- A grant from an FDA official, e.g., electronic communication. The FDA official may authorize shipment and use of the drug by telephone.
- A signed informed consent form from the subject or legally authorized representative unless both the investigator and a physician not participating in the treatment use certify in writing that:
  - The subject is confronted by a life-threatening situation where the use of the drug is necessary and there is no alternative therapy to save the life of the subject; AND
  - Informed consent cannot be obtained from the subject or the subject’s legal representative.
- Protocol or instructions for dose preparation
- Prescription or drug order

**NOTE:** Emergency use is an EXEMPTION from prior review and approval by the IRB.

10. **Controlled Substances**
   a) The Department of Pharmacy will follow the Health System Policy GR050 Use of Controlled Substances in Research, other institutional policies and applicable regulations.
   b) Controlled substance research medication will be stored in accordance with state and federal regulations.

11. **Reimbursement for Investigational Drug Service**
   a) The delegated pharmacist(s) will send invoices for investigational drug service to the Clinical Research Service Finance Core at CTOBilling@northwell.edu at least on a quarterly basis. (See Attachment 2)

**REFERENCES to REGULATIONS and/or OTHER RELATED POLICIES**
1. NWH Policy GR049: Medications and Investigational New Drugs (IND) used in Clinical Research
2. NWH Policy GR050: Use of Controlled Substances in Research

**CLINICAL REFERENCES**
N/A

**FORMS**

**ATTA**

**CHM**

**ENTS**
Invoice for Pharmacy Services Involving Investigational Drugs
Investigational Agent Participation Fee Schedule
| Reviewed / Approved by: LIJMC Pharmacy & Therapeutics Committee | 11/14/18 |
| Reviewed / Approved by: LIJMC Medical Board | 12/18/18 |

**Signatures on File:**

<table>
<thead>
<tr>
<th>X</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joseph Simpson, Chair, Pharmacy &amp; Therapeutics Committee</td>
<td></td>
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<tr>
<td>X</td>
<td>Date</td>
</tr>
<tr>
<td>Dana Rucco, Director of Pharmacy Services (LIJ)</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Date</td>
</tr>
<tr>
<td>Enrico Ligniti, Director of Pharmacy Services (CCMC)</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Date</td>
</tr>
<tr>
<td>Antonia Alafris, Director of Pharmacy Services (ZHH)</td>
<td></td>
</tr>
</tbody>
</table>

**VERSION HISTORY:** 6/16, 11/18
# INVOICE FOR PHARMACY SERVICES INVOLVING INVESTIGATIONAL DRUGS

(Please send the invoices to CRSBilling@NSHS.edu with “PHARMACY INVOICE - specify your site” in the subject line)

<table>
<thead>
<tr>
<th>Hospital or Medical Center</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Title</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Principal Investigator</strong></td>
<td><strong>Sponsor</strong></td>
</tr>
<tr>
<td><strong>Pharmacy Dept Account#</strong></td>
<td><strong>Peoplesoft#</strong></td>
</tr>
</tbody>
</table>

## Product Procurement Cost (Please attach the invoice)

*When the Department of Pharmacy purchases investigational products on behalf of the PI and designee*

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Cost to be reimbursed</th>
</tr>
</thead>
</table>

## Start-up or Set-up Fee

*The first dispensation for the first subject ONLY*

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
</table>

## Dispensation Records

<table>
<thead>
<tr>
<th>Period</th>
<th>Investigational Product 1</th>
<th>Investigational Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>From:</td>
<td>Dates</td>
<td>Dates</td>
</tr>
<tr>
<td>To:</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject Last Name, First Name Initial</th>
<th>Subject Date of Birth</th>
<th>Dates</th>
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</thead>
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<tr>
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</table>

<table>
<thead>
<tr>
<th>Annual Maintenance Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
</tr>
</tbody>
</table>

## Close-out Fee

*Last invoice ONLY*

<table>
<thead>
<tr>
<th>Date of Invoice</th>
<th>Pharmacist Name</th>
</tr>
</thead>
</table>

**Note:** Reimbursement is based on the original budget negotiated for each study.
# Investigational Agent Participation Fee Schedule

<table>
<thead>
<tr>
<th>PHARMACY STUDY SERVICE</th>
<th>Rate</th>
<th>Negotiated Contract*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Start-Up Initiation Fee (order and/or receive study medication, create and maintain</td>
<td>$1000 flat</td>
<td></td>
</tr>
<tr>
<td>accountability records, develop departmental-specific dispensing guidelines, meet</td>
<td></td>
<td></td>
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<tr>
<td>with investigator and/or study coordinator)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Randomization Schema Prepared by Pharmacy</td>
<td>$ 150 flat</td>
<td></td>
</tr>
<tr>
<td>3. Data Collection Sheet Prepared by Pharmacy</td>
<td>$ 150 flat</td>
<td></td>
</tr>
<tr>
<td>4. Single or Double Blinding Performed by Pharmacy</td>
<td>$ 150 / year</td>
<td></td>
</tr>
<tr>
<td>5. Dose Calculations Performed by Pharmacy</td>
<td>$ 150 / year</td>
<td></td>
</tr>
<tr>
<td>6. Randomization Performed by Pharmacy</td>
<td>$ 150 / year</td>
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</tr>
<tr>
<td>7. Annual Maintenance for Non-Controlled Substances (process orders, maintain</td>
<td>$500 / year</td>
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<tr>
<td>dispensing records, monitor integrity and storage requirements, maintain records of</td>
<td></td>
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<tr>
<td>returned agents, participate in planned or unplanned audits, provide administrative</td>
<td></td>
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<tr>
<td>support)</td>
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<tr>
<td>8. Annual Maintenance for Controlled Substances (process orders, maintain dispensing</td>
<td>$750 / year</td>
<td></td>
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<tr>
<td>records, monitor integrity and storage requirements, maintain records of returned</td>
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<tr>
<td>agents, participate in planned or unplanned audits, provide administrative support)</td>
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<tr>
<td>9. Low Intensity Dispensing: (no compounding, simple dispensing of one non-sterile</td>
<td>$ 5 per agent per</td>
<td></td>
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<tr>
<td>oral solid, liquid product per dose. Fee increase proportionately for additional doses</td>
<td>flat $500 / month</td>
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<tr>
<td>dispensed)</td>
<td></td>
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<tr>
<td>10. Moderate Intensity Dispensing: (simple sterile preparation requiring compounding)</td>
<td>$10 per agent per</td>
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<td></td>
<td>dose or flat $1000</td>
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<tr>
<td>11. High Intensity Dispensing: (complex sterile preparation requiring compounding or</td>
<td>$25 per agent per</td>
<td></td>
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<tr>
<td>preparation of bio-hazardous sterile products)</td>
<td>dose or flat $2500</td>
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<tr>
<td>12. Closing (reconcile inventories, return drugs, close out protocol)</td>
<td>$ 500 Flat</td>
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<tr>
<td>13. Principal Investigator Self-Storage Site Inspection Fee</td>
<td>$ 150 / year</td>
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<tr>
<td>(Investigational agents not housed in the Investigational Pharmacy proper but</td>
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<td>requires pharmacy oversight due to affiliation of practice with the NSLIH; confirming</td>
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<tr>
<td>state, federal and study requirements for storage, documentation and dispensing of</td>
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<tr>
<td>agents is meet)</td>
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*Minimum 1 year contract agreement. Any changes to protocol will require review of impact on pharmacy services.
### Systemic Anticoagulation with Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients

<table>
<thead>
<tr>
<th>Date</th>
<th>Study Day #</th>
<th>Quantity Dispensed</th>
<th>Administration Time</th>
<th>SCr (mG/dL)</th>
<th>eGFR (mL/min Reviewed</th>
<th>Pharmacist Initial &amp; Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM Dose</td>
<td>PM Dose</td>
<td>AM Dose</td>
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<td>PM Dose</td>
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</tbody>
</table>

**HEP-COVID TRIAL**

Protocol #: 20-0340  

**Patient Accountability Log**

Principal Investigator(s):  

Patient Name:  

MRN:  

Treatment Arm:  

Enoxaparin dose / frequency:  

At time of randomization:  

CrCl (mL/min):  

BMI (kg/m²):  

Subject ID:  

DOB:  

Date  

Study Day #  

Quantity Dispensed  

Administration Time  

SCr (mG/dL)  

eGFR (mL/min Reviewed)  

Pharmacist Initial & Date  

Comments
<table>
<thead>
<tr>
<th>AM Dose</th>
<th>PM Dose</th>
<th>AM Dose</th>
<th>PM Dose</th>
<th>AM Dose</th>
<th>PM Dose</th>
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Protocol Amendment History

The original version of the protocol was completed on 26 April 2020. There were 6 protocol amendments approved by the Northwell Health Institutional Review Board (IRB) on the following dates:

1 June 2020
5 August 2020
29 September 2020
12 January 2021
1 March 2021
23 March 2021 (final version)

Details of the amendment history are listed below.

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic or Section</th>
<th>Description of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 June 2020</td>
<td>4. STUDY POPULATION, 4.1.1 Inclusion Criteria, 4.1.1.1 Inclusion Criteria for Study Subjects, #6</td>
<td>The original criterion for respiratory rate &gt; 20 and hypoxemia with oxygen saturation &lt; 92% on room air was changed to “requirement for supplemental oxygen.” This was based on the observation that vital signs were documented at inconsistent – and often increased – intervals (due to nursing efforts to reduce frequency of patient exposure). Furthermore, it was observed that goal oxygen saturation was highly variable among treating physicians. Thus, it was clarified with study personnel that this criterion would encompass any perceived need for oxygen per investigator judgment, based on clinical findings and objective data.</td>
</tr>
<tr>
<td></td>
<td>4. STUDY POPULATION, 4.1.1 Inclusion Criteria, 4.1.1.1 Inclusion Criteria for Study Subjects, #7</td>
<td>The original criterion of D-dimer (Dd) &gt; 6.0 times the upper limit of normal (ULN) per local laboratory was changed to &gt; 4.0 times ULN. This was based on data from a large, retrospective study showing [1] that Dd &gt; 4x ULN conferred significantly increased risk of in-hospital venous thromboembolism (VTE) or mortality in coronavirus-19 (COVID-19) inpatients. This data supported earlier reports on the predictive value of Dd in this population [2]. Given the pragmatic nature of the trial, it was decided that this lower threshold would be adequate to enroll the target population.</td>
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<tr>
<td></td>
<td>14.7 Appendix G</td>
<td>The Data Safety and Monitoring Board (DSMB) charter was added to the protocol.</td>
</tr>
<tr>
<td></td>
<td>14.8 Appendix H</td>
<td>The DataMart Data Elements were added to the protocol.</td>
</tr>
<tr>
<td>Date</td>
<td>Section</td>
<td>Changes</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>5 August 2020</td>
<td>2. STUDY OBJECTIVES AND HYPOTHESIS, 2.3</td>
<td>Asymptomatic distal deep vein thrombosis (DVT) of the lower extremity at hospital day 10 + 4 was added as a secondary efficacy endpoint. This was based on data showing asymptomatic venous thromboembolism (VTE) may portend important clinical outcomes in acute medically ill hospitalized patients [3]. Sepsis-induced coagulopathy (SIC) score at 30 ± 2 days was removed as a secondary efficacy endpoint as there were other diagnostic secondary efficacy endpoints that more readily captured severity of illness.</td>
</tr>
<tr>
<td>5 August 2020</td>
<td>5. STUDY TREATMENTS, 5.1</td>
<td>Language describing dosing of enoxaparin for subjects in the therapeutic-dose arm was changed. This amendment specified that subjects would receive assigned dosing “at randomization” instead of “during the course of their hospitalization” as stated in the original version of the protocol. This updated language allowed for situations in which dosing of study drug could be changed during the course of hospitalization, for example, in the case of worsening renal function.</td>
</tr>
<tr>
<td>29 September 2020</td>
<td>8. SAFETY EVALUATION AND REPORTING, 8.4</td>
<td>Antiphospholipid studies were removed from the list of required laboratories on day of randomization. This was a pragmatic amendment, as the presumed incidence of thrombophilia in the population was very low and some study sites had limited resources for laboratory testing.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressant medications were added to the relevant medications to be captured at time of randomization.</td>
</tr>
</tbody>
</table>
9. STATISTICAL METHODS, 9.2
Analysis
The modified intent-to-treat (mITT) population was defined as equivalent to the safety (SAF) population described in earlier versions of the protocol. There were no changes in criteria or analyses.

<table>
<thead>
<tr>
<th>Date</th>
<th>Section and Subsection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 January 2021</td>
<td>2. STUDY OBJECTIVES AND HYPOTHESIS, 2.3</td>
<td>Study Endpoints, 2.3.2 Secondary Efficacy Endpoint</td>
</tr>
<tr>
<td>1 March 2021</td>
<td>2. STUDY OBJECTIVES AND HYPOTHESIS, 2.3</td>
<td>Study Endpoints, 2.3.2 Secondary Efficacy Endpoint</td>
</tr>
<tr>
<td>23 March 2021</td>
<td>2. STUDY OBJECTIVES AND HYPOTHESIS, 2.3 Study Endpoints, 2.3.2 Secondary Efficacy Endpoint</td>
<td>Extracorporeal membrane oxygenation (ECMO) was added as a secondary efficacy endpoint. Initiation of ECMO typically requires therapeutic-dose anticoagulation to prevent thrombosis within the cannulas of the patient circuit. The addition of ECMO as a secondary efficacy endpoint thus allowed for the initiation of therapeutic-dose anticoagulation without qualifying as a protocol violation.</td>
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<tr>
<td></td>
<td>9. STATISTICAL METHODS, 9.3 Efficacy Analyses, 9.3.4 Secondary Analyses, Multiple Thrombotic Events</td>
<td>Exploratory analyses of multiple thrombotic events were added to the Statistical Methods. During the trial it was noted that some subjects were diagnosed with multiple thrombotic events. In view of studies suggesting a role for thrombosis in mortality [4-5], the question of whether intensity of anti-thrombotic therapy could mitigate risk of multiple thrombotic events was posed. This was explored as two separate analyses: a comparison of incidence of thrombotic events in all subjects; a comparison of incidence of subsequent thrombotic events following a first event. Both analyses were conducted for mITT and PP sets.</td>
</tr>
</tbody>
</table>

References

Statistical Reporting Plan for

HEP-COVID, Biweekly and Full DSMB Reporting

Sponsor: Northwell Health and the Feinstein Institutes for Medical Research

Study Number: Northwell Health HRPP: 20-0340

Study Title: Systemic Anticoagulation with Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients (HEP-COVIDTrial)

Version Number: 1.0

Version Date: 20201007

Author

Biostatistician Jessica Thurston Date

DocuSigned by: Jessica Thurston
Signer Name: Jessica Thurston
Signing Reason: I am the author of this document
Signing Time: 08-Oct-2020 7:47 AM MDT
DC23C9C55815488DA8B9524F2C0D5B34
Approval

DSMB Chair
James Douketis

Statistician Member
John Kittelson

DSMB Member
Sam Schulman

Sponsor Contact
Alex Spyropoulos
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8. ASSESSMENTS AND OUTCOMES ....................................................................................... 7
9. ANALYSIS AND DISPLAY CONVENTIONS ......................................................................... 9
10. MOCK TABLE, FIGURE AND LISTING SHELLS ................................................................. 11
1. **Purpose**
   The purpose of this reporting plan is to describe the reporting of data as stipulated in the HEP- COVID Data Safety Monitoring Board (DSMB) Charter to support a biweekly key efficacy and safety data review, as well as open and closed DSMB reports and the Interim Analysis (IA) of COVID-19 patients receiving study treatments during hospitalization in HEP-COVID trial.

2. **Database Description**
   The following data sources will be used to create the final tables, figures, and listings:
   - Clinical study data
   - Medical Dictionary for Regulatory Affairs (MedDRA) Coded Serious Adverse Events (SAEs)

   Study sites will enter clinical data information in the Research Electronic Data Capture (REDCap) Clinical Database. Northwell Health and The Feinstein Institutes for Medical Research will provide transfers of all clinical data entered into the REDCap Clinical Database to CPC via a secure FTP site. In addition, Northwell Health and The Feinstein Institutes for Medical Research will also provide transfers of MedDRA coded SAEs of special interest report via a secure FTP site.

3. **Reporting Period and Frequency**
   The tables, figures, and listings described in this reporting plan which correspond to outputs for the biweekly key efficacy and safety data review will be provided to the DSMB Chair biweekly. The tables, figures and listings described in this reporting plan which correspond to outputs for the full safety meetings for the DSMB will occur at approximately 25%, 50%, 75%, and 100% of patient enrollment. The table described in this reporting plan which corresponds to the output for the IA will occur when the primary outcome is observed in approximately 50% of randomized patients.

4. **Analysis Sets**
   The Intent-To-Treat (ITT) Population will consist of all subjects that were randomized.

   The Safety (SAF) Population, consisting of all randomized patients who received at least one dose of the study drug will be used for reporting efforts of this plan. This is also known as the modified intent to treat population or mITT. Reporting of the SAF population will be done according to the majority treatment received (as treated), whereas analysis of the mITT population will be analyzed according to randomization assignment.

   The Per Protocol (PP) Population will consist of all patients who received at least 80% of planned therapy and did not have any major protocol deviations. Planned therapy will be calculated as the duration in days that the subject received study treatment according to randomization arm divided by the duration of hospitalization since randomization, in days. Major protocol deviations can be assessed from the database and will include:
- Did not meet inclusion criteria or met exclusion criteria
- Permanently discontinued assigned study medication after randomization not due to outcome event
- Did not undergo the Day 10+4 lower extremity (LE) Screening Doppler compression ultrasonography (CUS)

Planned therapy will be defined as:

*Duration in Days Subject Received Treatment (according to randomization arm)*

*Duration in Days of Hospitalization, since randomization*

Duration in Days that the subject received treatment will be defined as the study medication duration (days) at Day 30.

Duration in Days of Hospitalization, since randomization will be defined as:

*Last Date of Study Conduct – Date of Randomization*

The Last Day of Study Conduct will be defined as either:
- Date of discharge from hospital
- Date of Death
- Date of Day 30 evaluation

Whichever one of the above dates comes first will be utilized as the Last Date of Study Conduct.

Database specification of Planned Therapy for PP Population definition:

<table>
<thead>
<tr>
<th>Definition</th>
<th>Option</th>
<th>Database field(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration in Days Subject Received Treatment</td>
<td></td>
<td>d30_rx_antcg_hosp_stmdur</td>
</tr>
<tr>
<td>Last Date of Study Conduct</td>
<td>Date of Discharge</td>
<td>d104_date_of_discharge</td>
</tr>
<tr>
<td></td>
<td>Date of Death</td>
<td>d104_endp_dead_date, d30_endp_dead_date</td>
</tr>
<tr>
<td></td>
<td>Date of Day 30 Evaluation</td>
<td>d30_endp_followup_date</td>
</tr>
</tbody>
</table>

At the time of the interim analysis a completer subset will apply to mITT and PP Populations. Subjects in the mITT or PP that completed Day 30 ± 2 days as a face to face or telephonic visit, have died prior to Day 30, or if missing the Day 30 assessment, 30+2 days have passed since randomization, will be used at the time of interim analysis.

**Definition of Screening:**
Screening is defined as the period up to 72 hours prior to randomization.

**Definition of Randomization:**
Randomization is defined as the day the subject is randomized.
Definition of Hospital Day 10+4
Hospital Day 10 or sooner is defined as the tenth day following the date of hospital admission or at the time of hospital discharge.

Definition of Day 30 ± 2
Day 30 is defined as the thirtieth day following randomization.

Definition of First Event
The ‘First’ event for a subject will be defined as the first event of a type reported from the randomization date and Day 30+2, inclusive.

Definition of Study Medication
Categories 1 and 2 correspond to Treatment Arm 0. Categories 3-14 correspond to Prophylactic/Intermediate Dose Arm 1.
Categories 1 and 2 include the study medications: Enoxaparin 1 mg/kg SQ BID (CrCl ≥ 30ml/min) and Enoxaparin 0.5 mg/kg SQ BID (CrCl ≥ 15ml/min and < 30ml/min).
Categories 3-14 include the study medications: UFH 5000 IU SQ BID, UFH 5000 IU SQ TID, UFH 7500 IU SQ BID, UFH 7500 IU SQ TID, Enoxaparin 30 mg SQ QD, Enoxaparin 30 mg SQ BID, Enoxaparin 40 mg SQ QD, Enoxaparin 40 mg SQ BID, Enoxaparin 0.5 mg/kg SQ BID, Dalteparin 2500 IU QD, Dalteparin 5000 IU QD, and Other.

5. Reporting Scope
Unless otherwise specified, all patients included in the SAF population will be reported.

The reporting of these data will support a closed biweekly key efficacy and safety data review, as well as open and closed DSMB reports and the IA. The closed biweekly and closed DSMB reports and IA will present data according to treatment group, and the open DSMB report will present data overall and not by treatment group.

6. Handling of Missing Data
No imputations for missing data will be made. Data will be displayed as collected.

Since this is a report of live study data and data are continuously being collected, entered and monitored, the number and percent of subjects missing endpoint data at the time of the data cut will be included in output tables to give perspective on completeness of follow-up. Endpoint event data will be considered missing under two circumstances:
1) If the question “Has the patient reached an endpoint” is missing at both Day 10 and Day 30.
2) If the questions “Has the patient reached an endpoint” is Yes at either Day 10 or Day 30 and any of the following event questions are missing
   - Deep vein thrombosis (DVT)
   - Pulmonary embolism (PE)
   - Splanchnic vein thrombosis
   - Cerebral sinus thrombosis
- Other vein thrombosis
- Stroke
- Myocardial infarction (MI)
- Major adverse limb event (MALE)
- Systemic embolism
- Intracardiac thrombus
- Death
- Major bleeding
- Progression to acute respiratory distress syndrome (ARDS)
- Need for intubation
- Inability to be discharged from the Intensive Care/Coronary Care Unit

Missing cardiovascular event level questions will be reported if it occurs in more than 5% of the SAF population.

Missing medical history and concomitant medication will be reported if it occurs in more than 5% of the SAF population.

7. **Unblinding Considerations**

The DSMB will have ongoing access to unblinded information. The biweekly and closed DSMB reports and IA will be created in a semi-blinded fashion with treatment groups being referred to as Group A and B and the treatment key provided in a separate document.

The study subject, site Principal Investigators (PIs), Executive Committee (EC) and the Sponsor will be blinded to individual patient treatment assignments and will not have access to any reports of aggregate study data by treatment assignment.

8. **Assessments and Outcomes**

i. **Summary of Enrollment**

   Enrollment will be summarized overall for the biweekly report and by site for the open and closed DSMB report.

ii. **Summary of Demographics and Baseline Characteristics**

   Baseline demographics such as age, gender, race, ethnicity, and body mass index (BMI) will be summarized for the SAF population for the open and closed DSMB reporting efforts.

iii. **Summary of Major Bleeding**

   Major bleeding events identified using International Society of Thrombosis and Haemostasis (ISTH) criteria will be summarized for SAF population for the biweekly and open and closed DSMB reporting efforts.

iv. **Summary of Cardiovascular Events**

   Patient counts of cardiovascular events will be summarized for the SAF population for the biweekly and open and closed DSMB reporting efforts. The first event of each cardiovascular event will be reported.
v. Summary of Secondary Efficacy Endpoints
Patient counts of progression to ARDS, need for intubation, inability to be discharged from the Intensive Care/Coronary Care Unit will be summarized for the SAF Population for the open and closed DSMB reporting effort. This first event of each will be reported.

vi. Summary of Death
Subject counts of deaths and the cause of death will be summarized and listed for the SAF population for the biweekly and open and closed DSMB reporting efforts.

vii. Summary of Serious Adverse Events (SAEs)
If the SAE onset date is subsequent to study medication start date, the SAE will be considered treatment emergent. Only Treatment Emergent SAEs will be included in the reports.

Uncoded SAEs will be listed by subject and treatment group for the biweekly report.

SAEs will be coded using MedDRA. A patient will be counted only once per category of summarization (e.g., if a patient has multiple SAEs, the patient will only be counted once in the overall ‘Any SAE’ row and will be counted once in each row for the specific SAE category reported). Patient counts will be summarized and listed by system organ class (SOC) and preferred term (PT) for SAEs for the open and closed DSMB reporting efforts.

viii. Summary of Medical History
Medical history will be summarized for the SAF population for the open and closed DSMB reporting efforts.

ix. Summary of Concomitant Medication Usage
Concomitant medication will be summarized for the SAF population for the open and closed DSMB reporting efforts.

x. Summary Day 30 Patient Disposition
Patient disposition at Day 30 will be summarized for the SAF population for the open and closed DSMB reporting efforts. Summary of Day 30 patient disposition will include:

- Completion of Day 30 follow-up (Completed, Lost to follow-up, In-hospital death)

xi. Summary of Primary Clinical Endpoint at Interim Analysis
Primary Clinical Endpoint
The primary clinical endpoint is a composite of arterial thromboembolic events (including myocardial infarction, stroke, and systemic embolism), venous thromboembolism (including symptomatic DVT of the upper or lower extremity asymptomatic proximal DVT of the lower extremity (assessed by ultrasonography at Day 10±4), and PE, and all-cause mortality at or before Day
Analysis of the primary endpoint will be conducted in the Completer Subset of the PP population and will also be conducted in the Completer Subset of the mITT population.

Database specification of composite primary clinical endpoint:

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Event</th>
<th>Database field(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thrombotic events</td>
<td>MI</td>
<td>even_pr_ef_ate_mi= “Yes”</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>even_pr_ef_ate_strk= “Yes”</td>
</tr>
<tr>
<td></td>
<td>Systemic embolism</td>
<td>even_pr_ef_ate_sysemb= “Yes”</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Symptomatic DVT of upper or lower extremity</td>
<td>even_pr_ef_vte_dvt= “Yes” and even_pr_ef_vte_sympt= “Yes” and (even_pr_ef_vte_dvt_ue= “Yes” or even_pr_ef_vte_dvt_le= “Yes”)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic proximal DVT of the lower extremity</td>
<td>even_pr_ef_vte_dvt= “Yes” and even_pr_ef_vte_sympt= “No” and even_pr_ef_vte_dvt_le= “Yes” and even_pr_ef_vte_dvt_le_loc= “Proximal”</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>even_pr_ef_vte_pe= “Yes”</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>Death</td>
<td>even_pr_ef_death= “Yes”</td>
</tr>
</tbody>
</table>

Details of the IA are provided in Attachment 16.3 of the HEP-COVID DSMB Charter. The IA is anticipated to occur at or before the time when approximately 60% of subjects have been enrolled. For this analysis, the absolute risk of the composite endpoint will be summarized for each treatment group, the absolute risk reduction (ARR) will be reported, and the corresponding 1-sided p-value and confidence interval will be reported.

The interim analysis will allow early termination for evidence of efficacy if the absolute risk reduction (ARR) is -0.234 (23.4%) lower in the therapeutic dose group than in the prophylactic/intermediate dose group. The trial will stop for futility if the risk of an event is larger with therapeutic dosing than with prophylactic dosing. The study will continue to final analysis if the observed ARR is between -0.234 and 0.

9. **Analysis and Display Conventions**

Mock tables, figures and listing shells (TFLs) are provided to assist in the review of this reporting effort. Minor edits and additions which do not affect the content or meaning of either the text or shells (e.g. typos, spacing, etc.) will not constitute the need for an amendment to the plan. Major changes will require an amendment and will require approval. All changes that are made to the plan after the initial approval will be tracked on a Changes Log and will be maintained at CPC Clinical Research (CPC). Page numbers, paginations of tables, footnotes, and column categories are subject to change to reflect the actual data. The report will be uploaded to a secure FTP site that is accessible.
by the DSMB chair.

All programs created by CPC to produce TFLs will be programmed and validated according to CPC SOP-BDM-C-002: Developing Data Analysis Programs and CPC SOP-BDM-C-003: Statistical Validation. This section details the general conventions to be used for statistical reporting and presentation.

- All tables will have the respective population sample size in the column heading. For example, if a table reports data for the SAF population, N would represent all patients that entered into the SAF population. Within the table the “small n” will represent the number of patients within the population of interest who have non-missing data or data otherwise available for the summary measures of interest (i.e. the denominator for a subset of the overall population being presented in the summary).

- Summary of discrete variables will consist of the number and percent of responses in each category. All percentages will be rounded to one decimal place unless clearly specified. The count and percentage of responses will be presented in the form of XX (XX.X%), where the percentage is in parentheses. If the count is “0” then the percentage may not be presented to draw attention to the non-zero count cells. If zero percentages are displayed these will be shown as “0.0%”. If the percent is “100”, the decimal place may be dropped. In addition, the decimal place may also be dropped due to space constraints within a table where this does not impact the interpretation of the results. Leading zeros will be used for decimal values less than one. For example, “0.05” rather than “.05” will be used.

- The distribution of continuous variables will be summarized using means, standard deviations (SD), medians, minimums (or 25th percentile), and maximums (or 75th percentile). Ordinal variables will be summarized using categorical methods if the number of observed response categories is small (usually 4 or fewer) and with medians, minimums and maximums otherwise.

- Mean and median values will be presented to 1 decimal more than the data, SD values will be presented to 2 decimals more than the data, and minimum/maximum values will be presented to the same number of decimals as the data.

- Where entries in mock shells are in conflict with the above rules, then the above rules will take precedence, unless specified otherwise.
10. **Mock Table, Figure and Listing Shells**

**Table of Contents for Closed Biweekly Tables, Figures and Listings**

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title (Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Summary of Treatment Assignment Key (Randomized Subjects)</td>
</tr>
<tr>
<td>1</td>
<td>Summary of Enrollment (Randomized Subjects)</td>
</tr>
<tr>
<td>2</td>
<td>Summary of Major Bleeding Events (Safety Population)</td>
</tr>
<tr>
<td>3</td>
<td>Summary of Subject Counts of Cardiovascular Events (Safety Population)</td>
</tr>
<tr>
<td>4</td>
<td>Summary of Death (Safety Population)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Listing Number</th>
<th>Title (Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Serious Adverse Events of Special Interest (Safety Population)</td>
</tr>
</tbody>
</table>

**Table of Contents for DSMB Tables, Figures and Listings**

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title (Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Summary of Treatment Assignment Key (Randomized Subjects)</td>
</tr>
<tr>
<td>1a</td>
<td>Summary of Enrollment (Randomized Subjects)</td>
</tr>
<tr>
<td>1b</td>
<td>Summary of Enrollment by Site (Randomized Subjects)</td>
</tr>
<tr>
<td>2</td>
<td>Summary of Demographics and Baseline Characteristics (Safety Population)</td>
</tr>
<tr>
<td>3</td>
<td>Summary of Medical History, VTE risk factors recorded at randomization (Safety Population)</td>
</tr>
<tr>
<td>4</td>
<td>Summary of Medical History, Comorbidities recorded at randomization (Safety Population)</td>
</tr>
<tr>
<td>5</td>
<td>Summary of Clinical Scores (Safety Population)</td>
</tr>
<tr>
<td>6</td>
<td>Summary of Concomitant Medications and Treatments, COVID-19 Treatment at Randomization (Safety Population)</td>
</tr>
<tr>
<td>7</td>
<td>Summary of Concomitant Medications and Treatments, COVID-19 Treatment at Hospital Day 10 or Discharge (Safety Population)</td>
</tr>
<tr>
<td>8</td>
<td>Summary of Concomitant Medications and Treatments, COVID-19 Treatment at Day 30 (Safety Population)</td>
</tr>
<tr>
<td>9</td>
<td>Summary of Concomitant Medications and Treatments, Anticoagulants at Randomization (Safety Population)</td>
</tr>
<tr>
<td>10</td>
<td>Summary of Concomitant Medications and Treatments, Study Medication and Anticoagulants at Day 10 or Discharge (Safety Population)</td>
</tr>
<tr>
<td>11</td>
<td>Summary of Concomitant Medications and Treatments, Anticoagulant Prophylaxis at Day 30 (Safety Population)</td>
</tr>
<tr>
<td>12</td>
<td>Summary of Concomitant Medications and Treatments, Antiplatelet and Other Medications at Randomization (Safety Population)</td>
</tr>
<tr>
<td>13.1</td>
<td>Summary of Concomitant Medications and Treatments, Antiplatelet and Other Medications at Day 10 or Discharge (Safety Population)</td>
</tr>
<tr>
<td>13.2</td>
<td>Summary of Concomitant Medications and Treatments, Antiplatelet and Other Medications at Day 30 (Safety Population)</td>
</tr>
<tr>
<td>14.1</td>
<td>Summary of Concomitant Medications and Treatments, Mechanical thromboprophylaxis at Randomization (Safety Population)</td>
</tr>
<tr>
<td>14.2</td>
<td>Summary of Concomitant Medications and Treatments, Mechanical thromboprophylaxis at Day 10 or Discharge (Safety Population)</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title (Population)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Serious Adverse Events of Special Interest (Safety Population)</td>
</tr>
<tr>
<td>2</td>
<td>All-Cause Mortality (Safety Population)</td>
</tr>
</tbody>
</table>

Table of Contents for Interim Analysis Tables, Figures and Listings

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title (Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Summary of Treatment Assignment Key (Randomized Subjects)</td>
</tr>
<tr>
<td>1</td>
<td>Summary of Enrollment (Randomized Subjects)</td>
</tr>
<tr>
<td>2a</td>
<td>Analysis of Primary Clinical Endpoint (Per Protocol Population Completer Subset)</td>
</tr>
<tr>
<td>2b</td>
<td>Analysis of Primary Clinical Endpoint (Modified Intent-To-Treat Completer Subset)</td>
</tr>
</tbody>
</table>
## Table 0. Summary of Treatment Assignment Key
### All Randomized Subjects

<table>
<thead>
<tr>
<th>Closed Biweekly Treatment Group (A or B)</th>
<th>Treatment Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>xxxxxxxxx</td>
</tr>
<tr>
<td>X</td>
<td>xxxxxxxxx</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.#, #.#*

**Dataset(s): DS1, DS2**  **Program: Program name.sas**  **(Produced by CPC on <DDMMYYYY>)**  **Data Extraction Date: <DDMMYYYY>**

**Programming Note:** This table will be provided to the DSMB separate from the report tables.
### Table 1. Summary of Enrollment

**All Randomized Subjects**

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects in the ITT Population [1] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Safety Population [2] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Safety Population Completed Day 30 – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the PP Population [3]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Randomization strata</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>ICU [4]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Non-ICU [4]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

ITT=Intent-to-treat, mITT = modified intent-to-treat, PP=Per-Protocol

[1] ITT population consists of all randomized subjects
[2] Safety population consists of randomized subjects who received at least one dose of study drug (also known as modified intent to treat population or mITT).
[3] PP population consists of all randomized subjects who received 80% of the planned therapy and did not have any major protocol deviations.
[4] Denominator for percentages is the safety population by respective treatment group.

DataSource(s): #.##, #.##

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>
Table 2. Summary of Major Bleeding
Safety Population

<table>
<thead>
<tr>
<th>Major Bleeding Category [2]</th>
<th>A</th>
<th>B</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with at least one major bleed</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number (%) of subjects with missing bleeding status [1]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Total number of major bleeds</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Major Bleeding Category [2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in hemoglobin of 2g/dl or more within 24 hours [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Transfusion of 2 or more units of packed red blood cells [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Critical site bleeding (including intracranial, intraocular, intra-articular, retroperitoneal, intramuscular with component syndrome, pericardial) [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Intracranial Bleeding [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Bleeding that is fatal [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Bleeding that necessitates surgical intervention [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>[1] A missing bleeding status indicates that the question ‘Has the patient reached an endpoint’ is missing at both Day 10 and Day 30 or it is answered ‘Yes’ at either timepoint, but the Major Bleeding questions is missing.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[3] Denominator for percentages is the total number of major bleeds by respective treatment group.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source Listing(s): #.##, #.##
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYY>) Data Extraction Date: <DDMMMYYYY>
Table 3. Summary of Subject Counts of Cardiovascular Events
Safety Population

<table>
<thead>
<tr>
<th>Cardiovascular Event Category</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with missing cardiovascular event status [1]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cardiovascular Event Category [2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Pulmonary embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Splanchnic vein thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cerebral sinus thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other vein thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Hemorrhagic – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Ischemic – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fatal Stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Myocardial Infarction – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fatal Myocardial Infarction – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Major adverse limb event – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Major adverse limb event amputation – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Systemic embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>
### Intracardiac Thrombus – n (%)

<table>
<thead>
<tr>
<th></th>
<th>xx (xx.x%)</th>
<th>xx (xx.x%)</th>
<th>xx (xx.x%)</th>
</tr>
</thead>
</table>

[1] A missing cardiovascular event status indicates that the question ‘Has the patient reached an endpoint’ is missing at both Day 10 and Day 30.

[2] Only the first event of each cardiovascular event by subject will be reported. The ‘first’ event for a subject is defined as the first event reported from the randomization date and Day 30+2, inclusive.

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Myocardial Infarction – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other cardiovascular – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cancer-related – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Infectious/sepsis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Non-cardiovascular, non-cancer, non-infectious – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Unknown – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

[1] More than one cause of death can be reported per death.

<Source Listing(s): #.##, #.##>  
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYY>) Data Extraction Date: <DDMMYY>
Listing 1: Serious Adverse Events of Special Interest
Safety Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study ID</th>
<th>Reported Term/ Brief description</th>
<th>Onset Date/ End Date/ Last Date of Study drug Unexpected</th>
<th>Treatment Emergent [1]/ Category</th>
<th>Relationship to Study Intervention [2]</th>
<th>Action Taken/ Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>xxxxxxx</td>
<td>xxxxxxx/ xxxxx/</td>
<td>ddMMMyyyy/ ddMMMyyyy/</td>
<td>Yes/ xxxxx</td>
<td>xxxxx</td>
<td>xxxxx/ xxxxx</td>
</tr>
</tbody>
</table>

Sort order: Treatment, Subject, Onset Date

[1] Treatment Emergent is defined as any SAE which has an onset date that is subsequent to the date of randomization.


Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>). Data Extraction Date: <DDMMYYYY>
## Tables and Listings for Full DSMB Reports

### HEP COVID Closed DSMB Report

#### Table 0. Summary of Treatment Assignment Key

**All Randomized Subjects**

<table>
<thead>
<tr>
<th>Closed DSMB Treatment Group (A or B)</th>
<th>Treatment Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>xxxxxx</td>
</tr>
<tr>
<td>x</td>
<td>xxxxxx</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.##, #.##*

*Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>*

*Programming Note: This table will be provided to the DSMB separate from the report tables.*
# Table 1a. Summary of Enrollment
## All Randomized Subjects

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=xx)</td>
<td>(N=xx)</td>
<td>(N=xx)</td>
</tr>
<tr>
<td>Number of subjects in the ITT Population [1] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Safety Population [2] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Safety Population Completed Day 30 – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the PP Population [3]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

**Randomization strata**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU [4]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Non-ICU [4]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

ITT=Intent-to-treat, mITT = modified intent-to-treat, PP=Per-Protocol

[1] ITT population consists of all randomized subjects
[2] Safety population consists of randomized subjects who received at least one dose of study drug (also known as modified intent to treat population or mITT).
[3] PP population consists of all randomized subjects who received 80% of the planned therapy and did not have any major protocol deviations.
[4] Denominator for percentages is the safety population by respective treatment group.

Source Listing(s): #.##, #.##
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYY>) Data Extraction Date: <DDMMYY>
### Table 1b. Summary of Enrollment by Site

**All Randomized Subjects**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects in the ITT Population [2] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Safety population [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the PP Population [4]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

**Site 1**
- Number of subjects in the ITT population | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
- Number of subjects in the Safety population | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
- Number of subjects in the PP population | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

**Site 2**
- Number of subjects in the ITT population | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
- Number of subjects in the Safety population | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
- Number of subjects in the PP population | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

(continue for all sites)

---

**ITT=Intent-to-treat, mITT = modified intent-to-treat, PP=Per-Protocol**

[1] Denominator for percentages is the number of subjects enrolled in the corresponding population by treatment group.

[2] ITT population consists of all randomized subjects

[3] Safety population consists of randomized subjects who received at least one dose of study drug (also known as modified intent to treat population or mITT).

[4] PP population consists of all randomized subjects who received 80% of the planned therapy and did not have any major protocol deviations.

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

**Programming Note:** Repeat for the open DSMB report

**Programming Note:** The open DSMB report will only report on the ‘Overall’ group
## Table 2. Summary of Demographics and Baseline Characteristics
### Safety Population

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at hospital admission (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
<tr>
<td><strong>Gender – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Female</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Ethnicity – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Unknown/Declined</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Race – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Asian</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>White</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other/Multiracial</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Unknown/Declined</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Weight (kilograms)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
<tr>
<td><strong>Body Mass Index (kilograms per meter squared)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
<tr>
<td>Smoking (current) – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

SD= Standard deviation

(Source Listing(s): #.##, #.##)
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
### Table 3. Summary of Medical History, VTE Risk Factors Recorded at Randomization

**Safety Population**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of VTE – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Personal History of VTE – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of Cancer – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Solid Cancer – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Haemtaological Cancer – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Active Cancer – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Autoimmune Disease – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>ICU/CCU Stay – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Recent Surgery (&lt; 3 months) – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Recent Trauma – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Medical History Category</td>
<td>Yes (n)</td>
<td>No (n)</td>
<td>Missing (n)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>---------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hormonal therapy/OCP – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Known Thrombophilia – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of recent stroke with paresis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of severe infection (&lt;3 months) – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

**Source Listing(s): #.##, #.##
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYY>) Data Extraction Date: <DDMMMYYYY>

**Programming Note:** Repeat for the open DSMB report

**Programming Note:** The open DSMB report will only report on the ‘Overall’ group

**Programming Note:** If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category.
<table>
<thead>
<tr>
<th>Medical History/Comorbidities</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Cardiomyopathy/diminished left ventricular systolic function – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Heart failure with reduced EF – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Heart failure with preserved EF (EF &gt; 50%) – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Dyslipidemia – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Obesity – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Coronary artery disease – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>-------</td>
</tr>
<tr>
<td>Valvular heart disease – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of ischemic stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of carotid occlusive disease – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Peripheral arterial disease – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Active gastrointestinal ulcer – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of bronchiectasis/Pulmonary Cavitation – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Chronic renal disease – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Chronic lung disease – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Viral hepatitis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Chronic liver disease/Cirrhosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Thyroid disease – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Severe immobility – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Medical History Category</td>
<td>Yes (% of population)</td>
<td>No (% of population)</td>
<td>Unknown (% of population)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>History of bleeding (&lt; 3 months but &gt; 1 month) – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>History of bleeding (&lt; 3 months but &gt; 1 month), Minor or major [3] – n (%)</td>
<td>Minor: xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Major: xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Pulmonary hypertension – n (%)</td>
<td>Yes: xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No: xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

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**Source Listing(s):** #.##, #.##

**Dataset(s):** DS1, DS2

**Program:** Program name.sas (Produced by CPC on <DDMMYY>)

**Data Extraction Date:** <DDMMYY>

**Programming Note:** Repeat for the open DSMB report

**Programming Note:** The open DSMB report will only report on the ‘Overall’ group

**Programming Note:** If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category
### Table 5. Summary of Clinical Scores, Randomization Safety Population

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quick SOFA score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
<tr>
<td><strong>SIC score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
<tr>
<td><strong>IMPROVE VTE risk score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
</tbody>
</table>

SD= Standard deviation

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
## Table 6. Summary of Concomitant Medication and Treatment, COVID-19 Treatment at Randomization

Safety Population

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Remdesivir – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Favipiravir – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Lopinavir/Ritonavir – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Other antivirals– n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine– n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Chloroquine– n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>IVIG – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Interferon alfa-2b – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
<td>No xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Steroids (glucocorticoids) – n (%)</strong></td>
<td>Yes xx (xx.x%)</td>
<td>Yes xx (xx.x%)</td>
<td>Yes (xx.x%)</td>
</tr>
<tr>
<td>Medication</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Tocilizumab – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Sarilumab – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Famotidine – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>NSAID – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Anakinra – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other immunosuppresants – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other IL6/IL6R antagonist – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other IL1/IL1R antagonist – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other unblinded investigational agent – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.##, #.##*

_Dataset(s): _DS1, DS2_  **Program:** _<Program name.sas>_  (Produced by CPC on _<DDMMYYYY>_)_  **Data Extraction Date:** _<DDMMYYYY>_*

**Programming Note:** Repeat for the open DSMB report

**Programming Note:** The open DSMB report will only report on the ‘Overall’ group

**Programming Note:** If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category.
### Table 7. Summary of Concomitant Medication and Treatment, COVID-19 Treatment at Day 10 or Discharge
#### Safety Population

<table>
<thead>
<tr>
<th>Medication/Treatment</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Treatment – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Mechanical ventilation – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Antibiotics – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Remdesivir – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Favipiravir – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other antivirals– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Hydroxychloroquine– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Chloroquine– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>IVIG – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Drug</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Interferon alfa-2b – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Steroids (glucocorticoids) – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Tocilizumab – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Sarilumab – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Famotidine– n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>NSAID – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Anakinra – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other immunosuppressants – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other IL6/IL6R antagonist – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other IL1/IL1R antagonist – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other immunomodulatory</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other unblinded investigational agent – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

<Source Listing(s): #.##, #.##>

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group

Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category
<table>
<thead>
<tr>
<th>Medication/Treatment</th>
<th>Treatment (N=xx)</th>
<th>Prophylactic/Intermediate (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Remdesivir – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Favipiravir – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other antivirals– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Hydroxychloroquine– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Chloroquine– n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>IVIG – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Interferon alfa-2b – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Steroids (glucocorticoids) – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Medication</td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Tocilizumab – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Sarilumab – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Famotidine – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>NSAID – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Anakinra – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other immunosuppressants – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other IL6/IL6R antagonist – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other IL1/IL1R antagonist – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other immunomodulatory – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other unblinded investigational agent – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

<Source Listing(s): #.##, #.##>  
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYY>) Data Extraction Date: <DDMMMYYYY>
Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group

Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category.
### Table 9. Summary of Concomitant Medication and Treatment, Anticoagulants at Randomization

#### Safety Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prophylactic/Intermediate</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=xx)</td>
<td>(N=xx)</td>
<td>(N=xx)</td>
</tr>
</tbody>
</table>

Unfractionated heparin – n (%)

- **Yes**: xx (xx.x%)
- **No**: xx (xx.x%)

Low molecular weight heparin – n (%)

- **Yes**: xx (xx.x%)
- **No**: xx (xx.x%)

Fondaparinux – n (%)

- **Yes**: xx (xx.x%)
- **No**: xx (xx.x%)

<Source Listing(s): #.##, #.##>

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group

Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category
Table 10. Summary of Concomitant Medication and Treatment, Study Medication and Anticoagulants at Day 10 or Discharge Safety Population

<table>
<thead>
<tr>
<th>Treatment (N=xx)</th>
<th>Prophylactic/Intermediate (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is on study medication anticoagulant prophylaxis – n (%)</td>
<td>Yes xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Unfractionated heparin – n (%)</td>
<td>Yes xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Low molecular weight heparin – n (%)</td>
<td>Yes xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fondaparinux – n (%)</td>
<td>Yes xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

<Source Listing(s): #.##, #.##>
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYY>) Data Extraction Date: <DDMMYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group

Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category
### Table 11. Summary of Concomitant Medication and Treatment, Anticoagulant Prophylaxis at Day 30

**Safety Population**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (N=xx)</th>
<th>Prophylactic/Intermediate (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient is on study medication – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Non-hospitalized patient post-discharge – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Enoxaparin 40 mg SQ QD – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Rivaroxaban 10 mg QD – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Apixaban 2.5 mg BID – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Low dose aspirin – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Other anticoagulant – n (%)</strong></td>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.##, #.##*

*Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYY>) Data Extraction Date: <DDMMYY>*

**Programming Note: Repeat for the open DSMB report**

**Programming Note: The open DSMB report will only report on the ‘Overall’ group**

**Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category**
# Table 12. Summary of Concomitant Medications and Treatments, Antiplatelet and Other Medications at Randomization Safety Population

<table>
<thead>
<tr>
<th>Treatment (N=xx)</th>
<th>Prophylactic/Intermediate (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Clopidogrel – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Prasugrel – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Ticagrelor – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cangrelor – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Vorapaxar – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Statin – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.##, #.##*

*Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>*

*Programming Note: Repeat for the open DSMB report*

*Programming Note: The open DSMB report will only report on the ‘Overall’ group*

*Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category*
Table 13.1. Summary of Concomitant Medications and Treatments, Antiplatelet and Other Medications at Day 10 or Discharge
Safety Population

<table>
<thead>
<tr>
<th>Treatment (N=xx)</th>
<th>Prophylactic/Intermediate (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>No</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

| Aspirin – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|                | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

| Clopidogrel – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|                    | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

| Prasugrel – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|                  | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

| Ticagrelor – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|                   | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

| Cangrelor – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|                  | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

| Vorapaxar – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|                  | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

| Statin – n (%) | Yes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
|               | No  | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
Programming Note: The open DSMB report will only report on the ‘Overall’ group
Programming Note: If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category.
### Table 14.1. Summary of Concomitant Medications and Treatments, Mechanical Thromboprophylaxis at Randomization

**Safety Population**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prophylactic/Intermediate</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=xx)</td>
<td>(N=xx)</td>
<td>(N=xx)</td>
</tr>
<tr>
<td>IVC filter – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Intermittent pneumatic compression – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Graduated compression stockings – n (%)</td>
<td>Yes</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.##, #.##*

*Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYY>) Data Extraction Date: <DDMMYY>*

**Programming Note:** Repeat for Day 10 or discharge and Day 30

**Programming Note:** Repeat for the open DSMB report

**Programming Note:** The open DSMB report will only report on the ‘Overall’ group

**Programming Note:** If missing medical history occurs in more than 10% of the safety population, a ‘Missing’ category should be added below the ‘No’ category for the respective medical history category.
### Table 15.1. Summary of Treatment Exposure
#### Randomized Subjects

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Study Medication Group at Randomization</th>
<th>Study Medication Reported at Day 10+4</th>
<th>Study Medication Reported at Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (N=xx)</td>
<td>B (N=xx)</td>
<td>A (N=xx)</td>
</tr>
<tr>
<td></td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Enox 1 mg/kg SQ BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enox 0.5 mg/kg SQ BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic/Intermediate Dose Arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH 5000 IU SQ BID</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>UFH 5000 IU SQ TID</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>UFH 7500 IU SQ BID</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>UFH 7500 IU SQ TID</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Enox 30mg SQ QD</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Enox 30 mg SQ BID</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Enox 40 mg SQ QD</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Enox 40 mg SQ BID</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Enox 0.5 mg/kg SQ BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalte 2500 IU QD</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Dalte 5000 IU QD</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other prophylactic dose</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>
Table 15.2. Summary of Medication Duration, Hospital Duration, and Compliancy Randomized Subjects

<table>
<thead>
<tr>
<th>Study Medication Duration (Days)</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Medication Duration as Planned (Days) [1]</th>
<th>n</th>
<th>xx</th>
<th>xx</th>
<th>xx</th>
<th>xx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td></td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital Duration (Days)</th>
<th>n</th>
<th>xx</th>
<th>xx</th>
<th>xx</th>
<th>xx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td></td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent of Days Compliant with Planned Study Medication [2]</th>
<th>n</th>
<th>xx</th>
<th>xx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
<td>xx.x (xx.xx)</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>(Minimum, Maximum)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
<td>(xx, xx)</td>
</tr>
</tbody>
</table>

SD= Standard Deviation

[1] Calculated as the duration in days that the subject received study treatment according to randomization.

[2] Calculated as the duration in days that the subject received study treatment according to randomization arm divided by the duration of hospitalization in days.

(Percent of Days Compliant with Planned Study Medication= Study Medication Duration as Planned (Days) / Hospital Duration (Days))

<Source Listing(s): #.##, #.##> Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYY>) Data Extraction Date: <DDMMMYYYY>
Table 16. Summary of Major Bleeding Safety Population

<table>
<thead>
<tr>
<th></th>
<th>A  (N=xx)</th>
<th>B  (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with at least one major bleed</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number (%) of subjects with missing bleeding status [1]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td><strong>Total number of major bleeds</strong></td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td><strong>Major Bleeding Category [2]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in hemoglobin of 2g/dl or more within 24 hours [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Transfusion of 2 or more units of packed red blood cells [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Critical site bleeding (including intracranial, intraocular, intra-articular, retroperitoneal, intramuscular with component syndrome, pericardial) [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Intracranial Bleeding [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Bleeding that is fatal [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Bleeding that necessitates surgical intervention [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

[1] A missing bleeding status indicates that the question ‘Has the patient reached an endpoint’ is missing at both Day 10 and Day 30 or it is answered ‘Yes’ at either timepoint, but the Major Bleeding questions is missing.

[2] More than one category can apply to a single major bleeding episode

[3] Denominator for percentages is the total number of major bleeds by respective treatment group

<Source Listing(s): #.###, #.###> Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYY>) Data Extraction Date: <DDMMYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
Table 17. Summary of Subject Counts of Cardiovascular Events
Safety Population

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with missing cardiovascular event status [1]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cardiovascular Event Category [2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Pulmonary embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Splanchnic vein thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cerebral sinus thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other vein thrombosis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Hemorrhagic – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Ischemic – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fatal Stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Myocardial Infarction – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Fatal Myocardial Infarction – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Major adverse limb event – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Major adverse limb event amputation – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Systemic embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>
Intracardiac thrombus – n (%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%)

[1] A missing cardiovascular event status indicates that the question ‘Has the patient reached an endpoint’ is missing at both Day 10 and Day 30.
[2] Only the first event of each cardiovascular event by subject will be reported. The ‘first’ event for a subject is defined as the first event reported from the randomization date and Day 30+2, inclusive.

Source Listing(s): #.##, #.##
Dataset(s): DS1, DS2
Program: Program name.sas
Produced by CPC on DDMMMYYYY
Data Extraction Date: DDMMMYYYY

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
### Table 18. Summary of Secondary Endpoints  
**Safety Population**

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with missing secondary endpoint status [1]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Progression to ARDS – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Need for intubation – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Inability to be discharged from the Intensive Care/Coronary care unit – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

[1] A missing secondary endpoint event status indicates that the question ‘Has the patient reached an endpoint’ is missing at both Day 10 and Day 30.

*Source Listing(s): #.##, #.##*

*Dataset(s): DS1, DS2*  
*Program: Program name.sas (Produced by CPC on <DDMMYY>)*  
*Data Extraction Date: <DDMMYY>*

**Programming Note:** Repeat for the open DSMB report

**Programming Note:** The open DSMB report will only report on the ‘Overall’ group
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of subjects who died)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Pulmonary embolism – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Myocardial Infarction – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Stroke – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other cardiovascular – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Cancer-related – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Infectious/sepsis – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Non-cardiovascular, non-cancer, non-infectious – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Unknown – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

[1] More than one cause of death can be reported per death.

Source Listing(s): #.##, #.##

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
### Table 20. Summary of Subject Counts of Treatment Emergent Serious Adverse Events of Special Interest by System Organ Class and Preferred Term Safety Population

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with at least one TESAE</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>&lt;Uncoded&gt;</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>&lt;Uncoded&gt;</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>SOC 1</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>PT 1</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>PT 2</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

.. Continue for all SOCs and PTs

TESAE = Treatment Emergent Serious Adverse Event

Subjects are counted at most once per system organ class and at most once per preferred term.

Treatment Emergent is defined as any SAE which has an onset date that is subsequent to the date of randomization. MedDRA version xx.x

<Source Listing(s): #.##, #.##>

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYY>) Data Extraction Date: <DDMMMYYYY>

Programming Note: Sort by SOC and PT in descending order of incidence, then alphabetically

Programming Note: Percentages are calculated based on the number of subjects in each treatment group.

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
Table 21. Summary of Patient Disposition at Day 30
Safety Population

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the patient completed the 30-day follow-up – n (%)</td>
<td>Completed xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>In-hospital death xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Missing xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Vital status – n (%)</td>
<td>Dead xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Alive xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Missing Vital Status xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

Source Listing(s): #.##, #.##
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will only report on the ‘Overall’ group
### Listing 1. Serious Adverse Events of Special Interest

**Safety Population**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study ID</th>
<th>SOC/Preferred Term/Verbatim</th>
<th>Onset Date/End Date</th>
<th>Reported Term/Brief description</th>
<th>Treatment Emergent [1]/Unexpected</th>
<th>Relationship to Study Intervention</th>
<th>Action Taken/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxxxxxxx</td>
<td>xxxxxxxx</td>
<td>xxxxxxx/xxxxxx/xxxxxx/xxxxxx</td>
<td>ddMMMyyyy/ddMMMyyyy/ddMMMyyyy</td>
<td>xxxx/xxxx/xxxx</td>
<td>xxxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
</tbody>
</table>

... Sort order: Treatment, Subject, Onset Date

SOCS=System Organ Class

[1] Treatment Emergent is defined as any SAE which has an onset date that is subsequent to the date of randomization.


Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>). Data Extraction Date: <DDMMYYYY>

Programming Note: Repeat for the open DSMB report

Programming Note: The open DSMB report will not report Treatment group
## Listing 2: All-Cause Mortality

**Safety Population**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study ID</th>
<th>Death</th>
<th>Death date</th>
<th>Death location</th>
<th>Cause of death</th>
<th>Cardiovascular death [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxxxxxx</td>
<td>xxxxxx</td>
<td>Yes</td>
<td>ddMMMyyyy</td>
<td>In-hospital/Outpatient</td>
<td>xxxxx</td>
<td>Y/N</td>
</tr>
</tbody>
</table>

Sort order: Treatment, Study ID, Death date

[1] Cardiovascular death includes death due to pulmonary embolism, myocardial infarction, stroke, other cardiovascular cause, or unknown.

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYY>). Data Extraction Date: <DDMMMYYYY>
## Tables and Listings for Interim Analysis

**HEP COVID Interim Analysis**

### Table 0. Summary of Treatment Assignment Key
All Randomized Subjects

<table>
<thead>
<tr>
<th>Interim Analysis Treatment Group (A or B)</th>
<th>Treatment Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>xxxxx</td>
</tr>
<tr>
<td>x</td>
<td>xxxxx</td>
</tr>
</tbody>
</table>

*Source Listing(s): #.##, #.##*  
*Dataset(s): DS1, DS2*  
*Program: Program name.sas* (Produced by CPC on <DDMMYYYY>)  
*Data Extraction Date: <DDMMYYYY>*  
*Programming Note: This table will be provided to the DSMB separate from the report table.*
### Table 1. Summary of Enrollment
**All Randomized Subjects**

<table>
<thead>
<tr>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Overall (N=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects in the ITT Population [1]– n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Safety Population [2] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Completer Safety Population subset [3] – n (%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the PP Population [4]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Number of subjects in the Completer PP Population subset [5]</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

**Randomization strata**
- ICU [6] | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
- Non-ICU [6] | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |

**Notes:**
- ITT=Intent-to-treat, mITT = Modified intent-to-treat, PP=Per-Protocol
- [1] ITT population consists of all randomized subjects
- [2] Safety population consists of randomized subjects who received at least one dose of study drug (also known as modified intent to treat population or mITT).
- [3] Completer safety population subset consists of randomized subjects who received at least one dose of study drug (also known as modified intent to treat population or mITT), and that completed Day 30 + 2 days as a face to face or telephonic visit, have died prior to Day 30, or if missing the Day 30 assessment, 30+2 days have passed since randomization.
- [4] PP population consists of all randomized subjects who received 80% of the planned therapy and did not have any major protocol deviations.
- [5] Completer PP population subset consists of all randomized subjects who received 80% of the planned therapy and did not have any major protocol deviations, and that completed Day 30 +2 days or as a face to face or telephonic visit, have died prior to Day 30, or if missing the Day 30 assessment, 30+2 days have passed since randomization.
- [6] Denominator for percentages is the safety population by respective treatment group.

[@] Listing(s): #.##, #.##
Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMYYYY>) Data Extraction Date: <DDMMYYYY>
**Table 2a. Analysis of Primary Clinical Endpoint Per-Protocol Population Completer Subset**

<table>
<thead>
<tr>
<th></th>
<th>A (N=xx)</th>
<th>B (N=xx)</th>
<th>Difference Between Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of the primary clinical endpoint [1]</td>
<td>xx</td>
<td>xx</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(xx. x%)</td>
<td>(xx. x%)</td>
<td></td>
</tr>
<tr>
<td>Absence of the primary clinical endpoint [1]</td>
<td>xx</td>
<td>xx</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(xx. x%)</td>
<td>(xx. x%)</td>
<td></td>
</tr>
<tr>
<td>Absolute risk of the composite primary endpoint [1]</td>
<td>x.x</td>
<td>x.xx</td>
<td>x.xxx [2]</td>
</tr>
<tr>
<td></td>
<td>xx</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>95% CI for the ARR p-value [1]</td>
<td>(x.xxx, x.xxx)</td>
<td>x.xxx</td>
<td></td>
</tr>
</tbody>
</table>

[1] Primary clinical endpoint is the composite of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), venous thromboembolism (including symptomatic deep vein thrombosis of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity (assessed by ultrasound at Hospitalization Day 10+4 or discharge), non-fatal pulmonary embolism, and all-cause mortality at or before Day 30.

[2] Denotes the risk difference or absolute risk reduction (ARR) between the two groups.


The completer safety population subset consists of randomized subjects who received at least one dose of study drug (also known as modified intent to treat population or mITT), and that completed Day 30 + 2 days as a face to face or telephonic visit, have died prior to Day 30, or if missing the Day 30 assessment, 30+2 days have passed since randomization.

The completer per-protocol population subset consists of all randomized subjects who received 80% of the planned therapy and did not have any major protocol deviations, and that completed Day 30 +2 days or as a face to face or telephonic visit, have died prior to Day 30, or if missing the Day 30 assessment, 30+2 days have passed since randomization.

Dataset(s): <DS1, DS2> Program: <Program name.sas> (Produced by CPC on <DDMMMYYYYY>) Data Extraction Date: <DDMMYYYYYY>

Programming note: Repeat this for Table 3. Analysis of Primary Clinical Endpoint on the Modified Intent To Treat Completer subset