Official Title: 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)

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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)

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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 thromboprohylaxis, recent reports also suggest the failure to prevent thromboembolic events in these patients using standard or routine thromboprohylaxis 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 thromboprophyalxis 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 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.

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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 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 I)**

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/ 3mLvial 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 COVD-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 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.

	Efficacy Decision			Futility Decision		
	Observed	**CIlo**	**P-value**	**Observed**	**CIlo**	**P-value**
Interim Analysis	-0.234	(-0.338, -0.068)	0.0027	0.000	(-0.166, 0.105)	0.3750
Final Analysis	-0.117	(-0.234, 0.000)	0.0250	-0.117	(-0.234, 0.000)	0.0250

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 properties of the interim monitoring design.

True treatment effect		Statistical properties of the design		
P1	ARR	Power	Average Sample Size	Probability of early stopping
0.252	-0.168	0.804	216.6	0.239
0.210	-0.210	0.941	197.5	0.394
0.168	-0.252	0.988	173.8	0.587

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.

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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 evens) 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.

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14.1 Appendix A

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, thromboprohylaxis 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

	Value	**Points**
Platelets, K/µL	>100	0
	50-100	1
	<50	2
INR	<1.3	0
	1.3-1.7	1
	>1.7	2
D-Dimer, ng/mL	<400	0
	400-4000	2
	>4000	3
Fibrinogen, mg/dL	>100	0
	<100	1

14.3 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.

14.4 Appendix D

Quick SOFA Score

Assessment	qSOFA score
Low blood pressure (SBP ≤ 100 mmHg)	**1**
High respiratory rate (≥ 22 breaths/min)	**1**
Altered mentation (GCS ≤ 14)	**1**

14.5 Appendix E

The 7 Factor IMPROVE VTE RAM *(18)

VTE Risk Factor	Points for the Risk Score
Previous VTE	**3**
Thrombophilia**	**2**
Current lower limb paralysis or paresis***	**2**
Cancer******	**2**
Immobilization********	**1**
ICU/CCU stay	**1**
Age > 60 years	**1**

Abbreviations:

IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; VTE, venous thromboembolism; RAM, risk assessment model; [M1] 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

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

***including unblinded investigational agents for COVID-19**

**** SIC score, Quick SOFA score, IMPROVE VTE Risk score,**

14.7 Appendix G

DSMB Charter

14.8 Appendix H

DataMart Data Elements

Demographic	Past Medical History	Active Problems (H&P)	MEDS	History	Vitals/Physical Exam (consider all vitals later)	Labs (consider all labs later)
Patient Name DOB MRN Visit ID Facility Visit Type (ED vs. ED -> Inpatient) Mode of arrival (ED ADULT Triage Note) Arrival from (home vs. SNF vs. transfer - ED ADULT Triage Note) Date / Time of Visit Age Sex Race Ethnicity Patient home zip code Patient insurance Preferred Language to Address Healthcare (ED ADULT Triage Note) ED Attending ED Nurse ED Resident Team – LIJ COVID Rule Out (+ NSUH version)	Heart disease Immunocompromised Diabetes Chronic respiratory disease – Asthma, COPD Diabetes Hypertension Cancer All "Health Issues" <u>PMH / Baseline</u> Frailty measure <u>Laboratory</u> Multiple COVID test results <u>Imaging</u> Echocardiography impression (+ EF% discrete?, PMH of CHF vs. new/change)	All active problems	<u>PMH / Home Meds</u> ACEI ARB Insulin All home medication <u>Hospital Ordered Medications</u> ACEI ARB Vasopressors chloroquine Steroids Kaletra Interferon alfa-2b Remdesivir Favipiravir Actemra Kevzara Antivirals Antibiotics	International travel (discrete field: ED ADULT Triage Note "International travel within 21 days?") Smoking history Social Determinants of Health Screen results (Inpatient RN Screen - Sunrise) Charleston co-morbidity index (backend of Sunrise) Chief Complaint Symptoms – ROS	Temp (first, highest, lowest, median, last) Oxygen saturation (first, lowest, median, last) Respiratory rate (first, highest, median, last) Heart rate (first, highest, lowest, median, last) Blood Pressure (first, lowest, highest, median, last) BMI	CBC w/ diff (all results) CMP LDH acute kidney injury measure (back end Sunrise table *Micheal Qiu knows) RVP results ABGs DDimer procalcitonin Troponin CD3 CD4 CD8 CK-MB Hs-CRP IL-6 ESR Ferritin PT aptt urea

All care providers PCP Emergency Contact						

<u>Hospital Orders</u>	<u>Imaging</u> (w/ time and date stamps)	<u>Visit / Outcome Info</u>		
Mechanical vent order Vent flowsheet info (all patients have vent flowsheet while some will be missing an order) Transfer to higher level of care (MICU) Vent Data (Tidal Vol/PEEP/FiO2/Mode) Hemodialysis, PD, CRRT Oxygen therapy (nasal cannula, high flow, non-invasive) ECMO	x-ray impression CT chest impression (w and w/o contrast) CTA chest impressions	Length of Stay Current patient vs. discharge Discharge to [Facility/Home] Diagnoses: PNA, ARDS All discharge diagnoses Death Repeat Admission (is this a repeat admission within 30 days?)		

14.9 Appendix I
BRMS User Manual

15.0 Appendix J
External Agreement Contract

15.1 Appendix K
Investigational Drug Service – Standard Operating Procedure

15.2 Appendix L
Patient Drug Accountability Log