Title: InterMediate ProphylACtic versus Treatment Dose Anticoagulation in Critically Ill Patients with COVID-19: A Prospective Randomized Study (The IMPACT Trial)

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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

List of Abbreviations

AE	Adverse Event
AC	Anticoagulation
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
Bi-PAP	Bilevel Positive Airway Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CrCl	Creatinine Clearance
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CTSC	Clinical Translational Science Center
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
DVT	Deep Venous Thrombosis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HIT	Heparin-Induced Thrombocytopenia
HUD	Humanitarian Use Device
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ISTH	International Society of Thrombosis and Haemostasis
KDIGO	Kidney Disease Improving Global Outcomes
LDH	Lactate Dehydrogenase
LMWH	Low-Molecular-Weight Heparin
PHI	Protected Health Information
PI	Principal Investigator

PT	Prothrombin Time
REDCap	Research Electronic Data Capture
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SC	Subcutaneous
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction
UFH	Unfractionated Heparin
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
VTE	Venous Thromboembolism
VWF	Von Willebrand Factor
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title: InterMediate ProphylACtic versus Treatment Dose Anticoagulation in Critically Ill Patients with COVID-19: A Prospective Randomized Study (The IMPACT Trial)

Short Title: The IMPACT Trial

Clinical Phase: IV

Principal Investigator: Maria T. DeSancho, M.D., M.Sc.

Study Description: The purpose of this study is to determine if therapeutic dose anticoagulation (experimental group) improves 30-day mortality in participants with COVID-19 compared to those receiving the intermediate dose prophylaxis (control group). Following screening, subjects will be randomized 1:1 to intermediate dose prophylaxis or therapeutic anticoagulation treatment arms. Treatment will continue for 28 days with longer-term follow-up through 6 months.

Sample Size: N=186; 93 patients per cohort

Enrollment: The study will enroll 186 subjects and screen up to 300 subjects

Study Population: Adult patients with documented COVID-19 infection

Enrollment Period: 6 months

Intervention Description: Intermediate Dose Prophylaxis

- Enoxaparin 0.5 mg/kg subcutaneously every 12 hours if CrCl ≥30 ml/min
- Enoxaparin 0.5 mg/kg subcutaneously every 24 hours if CrCl less than 30 mL/min
- If patient develops acute kidney injury (defined by KDIGO guidelines): unfractionated heparin 7,500 units subcutaneously every 8 hours.
- Fondaparinux (if history of HIT) 2.5 mg daily subcutaneously

Therapeutic Anticoagulation

- Unfractionated heparin (UFH) to target anti-Xa level 0.3 – 0.7 IU/mL or aPTT (according to institutional protocol).
- Enoxaparin 1 mg/kg subcutaneously every 12 hours
- Argatroban (if heparin-induced thrombocytopenia [HIT]), dosed according to institutional protocol.
- Fondaparinux (if HIT and CrCl ≥50 ml/min) dosed by weight:
  - ≥100 kg: 10 mg daily
  - <100 kg but ≥50 kg: 7.5 mg daily
  - <50 kg: 5 mg daily

Primary Objective: To determine if therapeutic anticoagulation improves 30-day mortality in COVID-19 positive patients compared to intermediate dose prophylaxis.

Secondary Objectives:

1. To assess if therapeutic anticoagulation reduces the length of ICU stay.
2. To determine if therapeutic anticoagulation reduces the number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction, other) and micro thrombosis.
3. To evaluate if therapeutic anticoagulation leads to increase major and clinically relevant non-major bleeding events as defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria.

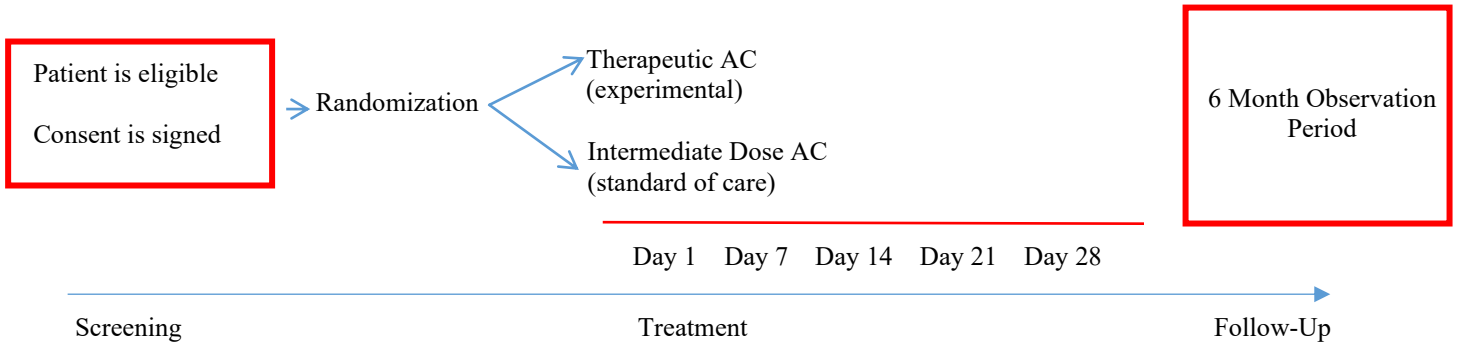
Primary Endpoints:

Efficacy Outcomes
Death at 30 days

Secondary Endpoints:

1- Length of ICU stay
2- Objectively documented pulmonary embolism (PE), proximal deep vein thrombosis (DVT) of the upper or lower extremities, thrombosis of the dialysis, continuous renal replacement (CRRT) filters; micro-thrombosis (skin biopsy), arterial thrombosis (stroke, myocardial infarction, limb ischemia)
3- Major bleeding, (as per ISTH guidelines), and clinically relevant non-major bleeding events.

1.1 Schema



1.2 Study Objectives and End Points

1.2.1 Primary Objectives

1. To determine if therapeutic anticoagulation improves 30-day mortality in COVID-19 positive patients compared to intermediate dose prophylaxis.

1.2.2 Secondary Objectives

1. To assess if therapeutic anticoagulation reduced the length of ICU stay.
2. To determine if therapeutic anticoagulation reduces the number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction other) and micro thrombosis.
3. To evaluate if therapeutic anticoagulation leads to increase major and clinically relevant non-major bleeding events as defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria.

1.2.4 Primary Endpoints

Efficacy Outcomes:

1. Death at 30 days

1.2.5 Secondary Endpoints

Safety Outcomes:

1. Length of ICU Stay
2. Objectively documented pulmonary embolism (PE), proximal deep vein thrombosis (DVT) of the upper or lower extremities, thrombosis of the

dialysis, continuous renal replacement (CRRT) filters, micro-thrombosis (skin biopsy), or arterial thrombosis (stroke, myocardial infarction, limb ischemia)

3. Major bleeding, defined (as per ISTH guidelines) as acute clinically overt bleeding associated with one or more of the following:
    a. A decrease in hemoglobin of 2 g/dL or more;
    b. A transfusion of 2 or more units of packed red cells;
    c. Bleeding that occurs in at least one of the following critical sites:
        i. Intracranial
        ii. Intra-spinal
        iii. Intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed)
        iv. Pericardial
        v. Intra-articular
        vi. Intramuscular with compartment syndrome
        vii. Retroperitoneal
    d. Bleeding that is fatal;
    e. Bleeding that necessitates surgical intervention.

    OR Clinically relevant non-major bleeding event, defined as acute clinically overt bleeding that does not meet the criteria for major and consists of;

    f. Any bleeding compromising hemodynamics;
    g. Spontaneous hematoma larger than 25cm^2, or 100cm^2 if there was a traumatic cause;
    h. Intramuscular hematoma documented by ultrasonography;
    i. Epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes;
    j. Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures;
    k. Hemoptysis, hematemesis, or spontaneous rectal bleeding requiring endoscopy or other medical intervention;
    l. Clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding;
    m. Permanent early discontinuation of the anticoagulant due to safety reasons

2. Background

2.1 Disease

The SARS-COV-2 (COVID-19) pandemic has had an unprecedented effect on our healthcare system and led to the death of over 164,939 people worldwide. Within the United States, New York State and specifically New York City has the highest number of COVID-19 infected patients. Why the pandemic carries a relatively high mortality rate across the world remains unclear, but there is growing evidence that COVID-19 triggers a hypercoagulable

state causing mostly microvascular thrombosis. A retrospective study in China showed that critically ill patients with markedly elevated D-Dimers who were on heparin or low-molecular weight heparin (LMWH) prophylactic-dose had lower mortality compared to those who did not receive pharmacologic thromboprophylaxis. At our own institution, pulmonary micro thrombi have been observed on autopsies and numerous skin biopsies of retiform purpura lesions on these patients have revealed thrombotic vasculopathies. In some countries, the dose of heparin or LMWH is being escalated to a therapeutic dose. Whether therapeutic-dose anticoagulation improves outcomes in these critically ill COVID-19 patients has not been studied.

2.2 Investigational Agent

All of the drugs described in this protocol are FDA approved for the intended indications and can be obtained through a prescription.

Enoxaparin (Lovenox®) is an anticoagulant medication approved by the FDA for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism. Enoxaparin is available as an injectable and is delivered subcutaneously. For this study, subjects randomized to the intermediate dose prophylaxis arm will receive Enoxaparin 0.5 mg/kg subcutaneously every 12 hours if their creatinine clearance is $\geq$ 30 ml/min. Subjects with creatinine clearance of < 30 ml/min will receive Enoxaparin 0.5 mg/kg subcutaneously every 24 hours. Subjects randomized to the therapeutic anticoagulation arm will receive Enoxaparin 1 mg/kg subcutaneously every 12 hours if their creatinine clearance is $\geq$ 30 ml/min and 1 mg/kg subcutaneously every 24 hours if creatinine clearance of < 30 ml/min.

Heparin sodium (unfractionated heparin) is an anticoagulant indicated for the prophylaxis and treatment of venous thromboembolism. For this study, subjects on the intermediate dose prophylaxis arm who develop acute kidney injury, as defined by the KDIGO guidelines, may receive unfractionated heparin 7,500 units subcutaneously every 8 hours. Subjects on the therapeutic anticoagulation arm may receive unfractionated heparin intravenous continuous infusion to target anti-Xa level of 0.3 – 0.7 IU/mL or therapeutic range aPTT, according to institutional guidelines.

Argatroban is a synthetic direct thrombin inhibitor that is approved for the prophylaxis and treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). Subjects randomized to the therapeutic anticoagulation arm with a history of HIT may receive argatroban dosed according to institutional protocol.

Fondaparinux (Arixtra®) is a synthetic and specific inhibitor of Factor X (Xa) indicated for the prophylaxis and treatment of deep vein thrombosis or acute pulmonary embolism. Subjects randomized to the intermediate dose prophylaxis arm with a history of HIT will receive fondaparinux 2.5 daily subcutaneously. Subjects randomized to the therapeutic anticoagulation arm with a history of HIT and creatinine clearance of ≥50 ml/min may receive fondaparinux dosed according to weight: if ≥100 kg, 10 mg daily subcutaneously; if <100 kg but ≥50 kg, 7.5 mg daily subcutaneously; if <50 kg, 5 mg daily subcutaneously.

More information about these agents may be obtained through their package inserts; see Appendix A for further details.

The researchers are requesting an IND exemption for this study as it involves off-label use of FDA-approved medications and will not be applying for a label change.

2.3 Rationale

Venous thromboembolism is a common complication in critically ill patients. Recent publications have demonstrated that the risk of thrombosis (venous, arterial and microthrombosis) in ICU patients with COVID-19 is 31% in a study from Holland despite prophylactic anticoagulation and 25% (venous thrombosis) in a study from China (without prophylactic anticoagulation). In a prospective cohort study from France, there were sixty-four clinically relevant thrombotic complications diagnosed in 150 patients with COVID-19 ARDS during their ICU stay, mainly pulmonary embolisms (25 patients, 16.7%). Based on above published data, we will compare 2 doses of parenteral anticoagulation (intermediate and therapeutic dose) in critically ill patients with COVID-19 infection.

In this study, intermediate dose prophylaxis will be considered the standard of care arm based on experience from the ICU at Weill Cornell Medicine and published data on standard prophylactic dose anticoagulation. The therapeutic anticoagulation arm will be considered experimental.

The D-dimer entry criteria of greater than or equal to 6 times the upper limit or normal was chosen based on published data from Cui et al. D-Dimers are checked on a daily basis as it is being done now in the ICU at WCM.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Enoxaparin, heparin, argatroban and fondaparinux are FDA approved parenteral anticoagulants used to prevent and treat VTE. The main side effect of anticoagulation is bleeding, therefore close monitoring of anticoagulation is required.

Further risks and known side effects of the various anticoagulants being used in this protocol may be found in the package inserts, located in Appendix A.

2.4.2 Known Potential Benefits

Critically ill patients with COVID-19 have an increased risk of death, but some studies have shown evidence that this risk has been decreased with the use of parenteral anticoagulation. We believe there will be a lower risk of VTE and other thrombotic events with the use of intermediate dose prophylaxis and therapeutic dose anticoagulation.

2.4.3 Assessment of Potential Risks and Benefits

Hospitalized patients typically receive standard-dose prophylactic anticoagulation to prevent the risk of developing thrombosis throughout their admission. From

April 5, 2020 patients who have required ICU-level care for treatment of COVID-19 in our hospital have been receiving intermediate dose prophylactic anticoagulation due to the observation of higher thrombosis risk noted in critically ill COVID-19 infected patients. Therapeutic dose anticoagulation may be warranted providing that the benefits outweigh the bleeding risk. We hope that this study will provide evidence that higher dose (therapeutic) anticoagulation is more efficacious and as safe as intermediate dose prophylaxis for prevention of thrombosis in critically ill patients with COVID-19 infection.

2.5 Correlative Studies Background

Additional blood will be collected for correlative studies to further assess the pathophysiology of thrombosis in these patients including: thrombin generation assay, plasmin generation, platelet activation assay, clot lysis time, annexin2.

3. Study Design

3.1 Overall Design

Prospective phase IV, open-label randomized control trial comparing two different doses of parenteral anticoagulation (Intermediate vs. therapeutic dose) in critically ill patients with COVID-19 infection. The purpose of the study is to determine if therapeutic dose anticoagulation improves 30-day mortality in COVID-19 positive patients compared to intermediate dose prophylaxis. Patients will be randomized 1:1 to either intermediate dose prophylaxis (standard of care arm) or therapeutic-dose anticoagulation (experimental arm). Each arm will enroll 93 patients, for a total of 186 patients Treatment on both arms will be for 28 days continuously. Patients will enter the study at the time of hospital admission. Patients will be recruited by their treating physician in the hospital or by the principal investigator.

Intermediate dose prophylaxis:

- If CrCl ≥30 ml/min, Enoxaparin 0.5 mg/kg SC every 12 hours
- If CrCl less than 30 ml/min, Enoxaparin 0.5 mg/kg SC every 24 hours
- If patient develops acute kidney injury (defined by KDIGO guidelines): unfractionated heparin 7,500 units SC every 8 hours
- If patient has a history of HIT, Fondaparinux 2.5 mg daily subcutaneously

For patients receiving Enoxaparin, adjust dose based on anti-Xa activity 4 hours after 3rd dose; goal of 0.4 – 0.6 IU/mL for intermediate prophylactic dose.

Therapeutic anticoagulation:
Full dose parenteral anticoagulation per institutional protocol:

- Enoxaparin 1 mg/kg SC every 12 hours If CrCl equal or more than 30 mL/min to target peak anti-Xa level 4 hours after the 3rd dose; goal 0.6 - 1.0 IU/mL
- Enoxaparin 1 mg/Kg SC every 24 hours If CrCl less than 30 mL/min to target peak anti-Xa level 4 hours after the 3rd dose; goal 0.6 - 1.0 IU/m
- If patient develops acute kidney injury (defined by KDIGO guidelines): Unfractionated heparin (UFH) to target anti-Xa level 0.3 – 0.7 IU/mL or aPTT (according to institutional protocol)

- If patient has a history of HIT or develops HIT:
    - Fondaparinux (if CrCl ≥50 ml/min).
        - If patient weight is ≥100 kg, 10 mg daily
        - If patient weight is <100kg but ≥50 kg, 7.5 mg daily
        - If patient weight is <50 kg, 5 mg daily
    - Or Argatroban if CrCl <50 ml/min), dosed according to institutional protocol.

Therapeutic dose adjusted per NYP Infonet protocols.

3.2 Scientific Rationale for Study Design

The risk of thrombosis in ICU patients with COVID-19 is 31% in a study from Holland despite prophylactic anticoagulation and 25% in a study from China (without prophylactic anticoagulation) and 43% in a French study despite prophylactic anticoagulation. Therefore we will compare 2 doses of parenteral anticoagulation (intermediate and therapeutic dose) in critically ill patients with COVID-19 infection.

3.3 Justification for Dose

We will compare an intermediate dose (high prophylactic-dose) vs. therapeutic dose anticoagulation in COVID-19 critically ill patients because significant risk of thrombosis was still observed with the standard prophylactic dose of anticoagulation.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the **Schedule of Assessments (SoA), Section 6.1**. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. Subject Selection

4.1 Study Population

Adult subjects with COVID-19 infection will be eligible for this study.

4.2 Inclusion Criteria

1. Age > 18 years old
2. COVID-19 positive on RT-PCR nasopharyngeal swab, or suspected COVID-19 infection with detectable SARS-CoV-2 IgG or IgM.

   NOTE: COVID-19 will be defined according to the World Health Organization (WHO) case definition for a “confirmed case”, which is a positive laboratory test for SARS-CoV-2, irrespective of clinical signs and symptoms. WHO reference laboratories currently use reverse transcription polymerase chain reaction (RT-PCR) tests to detect the presence of SARS-CoV-2 viral RNA.

3. ICU patient or non-ICU patient on invasive mechanical ventilation, BiPAP, 100% non-rebreather mask, or high-flow O_2, or supplemental O_2 of at least 4 liters per minute nasal cannula.
4. D dimer $\geq$ 700 ng/mL (3 times the upper limit of normal)

4.3 Exclusion Criteria

1. Objectively documented deep vein thrombosis or pulmonary embolism.
2. Patients in whom there is very high suspicion for pulmonary embolism and are on full-dose anticoagulation as per the treating physician.
3. Platelets <30,000 not due to disseminated intravascular coagulation (DIC), based on ISTH criteria and ASH FAQ (Appendix B).
4. Active bleeding that poses a contraindication to therapeutic anticoagulation in the opinion of the investigator.
5. History of bleeding diathesis (e.g., hemophilia, severe von Willebrand Disease, severe thrombocytopathy)
6. History of intracranial hemorrhage in the last 90 days
7. History of ischemic stroke in the past 2 weeks
8. Major neurosurgical procedure in the past 30 days
9. Cardiothoracic surgery in the past 30 days
10. Intra-abdominal surgery in the past 30 days
11. Intracranial malignancy
12. Patients who require therapeutic anticoagulation for other reasons like atrial fibrillation, deep venous thrombosis, pulmonary embolism, or antiphospholipid syndrome.

4.4 Lifestyle Considerations

Not applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a D-dimer level of <1400 ng/mL may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

See Table 1. Schedule of trial events.

Table 1. Schedule of trial events

	Screening *(within 48 hours of treatment initiation)*	Randomization	Treatment						Follow-Up	
			Day 1	Day 7	Day 14	Day 21	Day 28	30 days post-treatment *(+/- 2 days)*	60 days post-treatment *(+/- 2 days)*	6 months post-treatment *(+/- 7 days)*
Treatment[6]			X---------->							
Informed Consent	X									
Randomization		X								
Demographics	X									
Medical History[1]	X									
Treatment Initiation			X							
Vital Signs[2]	X		X	X	X	X	X	X	X	X
CBC w/ diff, platelets	X		X	X	X	X	X	X	X	X
PT, aPTT	X		X	X	X	X	X	X	X	X
D-Dimer	X		X	X	X	X	X	X	X	X
Fibrinogen	X		X	X	X	X	X	X	X	X
Serum Chemistry[3]	X		X	X	X	X	X	X	X	X
FVIII/VWF[4]		X					X		X	X
Activated Protein C Resistance		X					X		X	X
Lupus Anticoagulant aPTT lupus insensitive		X							X	X
Anticardiolipin		X							X	X
Anti-B2 Glyocprotein-1		X							X	X
Correlative Samples[5]		X							X	X
Vital Status								X	X	X
Adverse Event Evaluation	X	X	X---------->							
Concomitant Medications	X	X	X---------->							

1. Including information on symptoms of VTE, site and confirmatory tests, arterial thrombosis or microvascular thrombosis, type of anticoagulant/antiplatelet treatment and other treatment.
2. Body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask (as applicable).
3. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
4. VWF (von Willebrand Factor)
5. Two 3mL blue sodium citrate tubes. Randomization sample will be drawn prior to initiation of study treatment.
6. Treatment will be given every day for Day 1-Day 28; see section 7.7 for specific dosing schedules.

6.1.1 Screening and Randomization

6.1.1.1 Screening (within 48 hours of treatment initiation)

- Informed Consent
- Medical history, including information on symptoms of VTE, site and confirmatory tests, arterial thrombosis or microvascular thrombosis, type of anticoagulant/antiplatelet treatment and other treatment.
- Demographics
- Vital Signs (body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask [as applicable])
- Labwork (results must be available prior to enrollment and randomization)
  - CBC w/ diff, platelets
  - PT, PTT
  - D-dimer
  - Fibrinogen
  - Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium)
- Adverse Event Evaluation
- Concomitant Medications

6.1.1.2 Randomization (prior to treatment initiation)

- Randomization
- Labwork (results not required for randomization)
  - FVIII, VWF
  - Activated Protein C Resistance
  - Lupus Anticoagulant
  - aPTT lupus insensitive
  - Anticardiolipin
  - Anti-B2 Glycoprotein-1
  - Two 3 mL blue sodium citrate tubes of plasma for correlative studies
- Adverse Event Evaluation
- Concomitant Medications

6.1.2 Treatment Phase

Eligible subjects will be randomly assigned to Intermediate Prophylaxis Dose or Therapeutic Anticoagulation treatment groups in a 1:1 ratio. Treatment will continue for 28 days continuously.

6.1.2.1 Visit 1 (Day 1)

- Treatment initiation

- Vital Signs (body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask [as applicable])
- Labwork
  - CBC w/ diff, platelets
  - PT, PTT
  - D-dimer
  - Fibrinogen
  - Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium)
  - FVIII, VWF
- Activated Protein C ResistanceAdverse Event Evaluation
- Concomitant Medications

6.1.2.2 Visits 2 through 5 (Day 7, Day 14, Day 21, Day 28)

- Vital Signs (body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask [as applicable])
- Labwork
  - CBC w/ diff, platelets
  - PT, PTT
  - D-dimer
  - Fibrinogen
  - Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium)
- Adverse Event Evaluation
- Concomitant Medications

6.1.3 Follow-up Phase

Following completion of treatment, subjects will enter a 6-month follow-up period.

6.1.3.1 Visit 6 (30 Days Post-Treatment)

- Vital Signs (body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask [as applicable])
- Labwork
  - CBC w/ diff, platelets
  - PT, PTT
  - D-dimer
  - Fibrinogen
  - Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium)
- Adverse Event Evaluation

- Concomitant Medications
- Vital Status

6.1.3.2 Visit 7 (60 Days Post-Treatment)

- Vital Signs (body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask [as applicable])
- Labwork
  - CBC w/ diff, platelets
  - PT, aPTT
  - D-dimer
  - Fibrinogen
  - Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium)
  - FVIII, VWF
  - Activated Protein C Resistance
  - Lupus Anticoagulant
  - aPTT lupus insensitive
  - Anticardiolipin
  - Anti-B2 Glycoprotein-1
  - Two 3 mL blue sodium citrate tubes of plasma for correlative studies
- Adverse Event Evaluation
- Concomitant Medications
- Vital Status

6.1.3.3 Visit 8 (6 Months Post-Treatment)

- Vital Signs (body weight, blood pressure, heart rate, O2 saturation, mechanical ventilation, Bi-PAP, high flow O2, 100% non-rebreather mask [as applicable])
- Labwork
  - CBC w/ diff, platelets
  - PT, PTT
  - D-dimer
  - Fibrinogen
  - Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium)
  - FVIII, VWF
  - Activated Protein C Resistance
  - Lupus Anticoagulant
  - aPTT lupus insensitive
  - Anticardiolipin
  - Anti-B2 Glycoprotein-1
  - Two 3 mL blue sodium citrate tubes of plasma for correlative studies
- Adverse Event Evaluation
- Concomitant Medications

- Vital Status

7. Study Intervention

7.1 Study Intervention Description

Lovenox® (Enoxaparin sodium) is an anticoagulant medication approved by the FDA for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism. Enoxaparin is available as an injectable and is delivered subcutaneously. Enoxaparin is contraindicated in patients with active major bleeding and a history of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies.

Heparin sodium (unfractionated heparin) is an anticoagulant indicated for the prophylaxis and treatment of venous thromboembolism and pulmonary embolism. The use of unfractionated heparin is contraindicated in patients with a history of heparin-induced thrombocytopenia, patients in an uncontrolled bleeding state except when due to disseminated intravascular coagulation, and in patients who cannot have suitable blood coagulation tests performed at appropriate intervals.

Argatroban is a synthetic direct thrombin inhibitor that is approved for the prophylaxis or treatment of thrombosis in adult patients with heparin-inducted thrombocytopenia (HIT). Argatroban is contraindicated in patients with major bleeding.

Fondaparinux (Arixtra®) is a synthetic and specific inhibitor of Factor X (Xa) indicated for the prophylaxis and treatment of deep vein thrombosis or acute pulmonary embolism. It is supplied as a sterile, preservative-free injectable solution for subcutaneous use.

7.2 Availability

All drugs described in this protocol are FDA approved for the intended indications and can be obtained through a prescription.

7.3 Acquisition and Accountability

All drugs administered while subjects are hospitalized will be documented in the electronic medical records system. Any drugs taken at home by the subject will be documented in a study-specific drug diary and reviewed with the subject's treating physician at their next clinic visit.

7.4 Formulation, Appearance, Packaging, and Labeling

Lovenox® (Enoxaparin) is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5. Lovenox® is a clear, colorless to pale yellow sterile solution that may be administered by intravenous or subcutaneous injection only. Lovenox® is manufactured by Sanofi.

Heparin sodium (unfractionated heparin) is available in 0.45% Sodium Chloride Injection and 5% Dextrose Injection.

Argatroban Injection in 0.9% sodium chloride is a clear, colorless to pale yellow solution. It is supplied as a single use vial containing 125 mg argatrobain in 125 mL of aqueous sodium chloride solution (1 mg/mL). Argatroban Injection is manufactured by Sandoz, Inc.

Arixtra® (fondaparinux sodium) is supplied as a sterile, preservative-free injectable solution for subcutaneous use. Each single dose, prefilled syringe, affixed with an automatic needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 mL, 5.0 mg of fondaparinux sodium in 0.4 mL, 7.5 mg of fondaparinux sodium in 0.6 mL or 10.0 mg of fondaparinux sodium in 0.8 mL of an isotonic solution of sodium chloride and water for injection. The final drug product is a clear and colorless to slightly yellow liquid with a pH between 5.0 and 8.0. Arixtra® is manufactured by GlaxoSmithKline.

7.5 Product Storage and Stability

Lovenox® should be stored at 25°C with excursions permitted to 15°C-30°C (59°F-86°F). Do not store multiple-dose vials for more than 28 days after the first use.

Heparin sodium should be stored at 20°C to 25°C (68°F-77°F). Avoid excessive heat. Do not freeze.

Argatroban vials should be stored in their original cartons at 20°-25° C (68°-77°F). The product should be retained in the original carton to protect from light. Do not freeze.

Arixtra® (fondaparinux sodium) should be stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F).

7.6 Preparation

See Appendix A for package inserts of each drug used in this protocol.

7.7 Dosing and Administration

All subjects will be dosed continuously for 28 days. Specific dosing instructions per drug and per arm are as follows:

Intermediate Dose Prophylaxis arm:
Subjects randomized to the Intermediate Dose Prophylaxis arm will receive one of the following treatments:

- If CrCl $\geq$30 ml/min, Enoxaparin 0.5 mg/kg subcutaneously every 12 hours
- If CrCl less than 30 ml/min, Enoxaparin 0.5 mg/kg subcutaneously every 24 hours
- If patient develops acute kidney injury (defined by KDIGO guidelines): unfractionated heparin 7,5000 units subcutaneously every 8 hours.
- If patient has history of HIT, fondaparinux 2.5 mg daily subcutaneously

For subjects receiving Enoxaparin, adjust dose based on anti-Xa activity 4 hours after the 3rd dose; goal of 0.4 – 0.6 IU/mL.

Therapeutic Anticoagulation arm:
Full dose parenteral anticoagulation per institutional protocol:

- Enoxaparin 1 mg/kg subcutaneously every 12 hours if CrCl ≥30mL/min.
- Enoxaparin 1 mg/kg subcutaneously daily if CrCl <30 mL/min.
- If AKI develops, Unfractionated heparin (UFH) to target anti-Xa level 0.3 – 0.7 IU/mL or aPTT (according to institutional protocol).
- Argatroban (if heparin-induced thrombocytopenia [HIT] and CrCl <50 ml/min), dosed according to institutional protocol.
- Fondaparinux (if HIT and CrCl ≥50 ml/min), dosed according to patient weight:
  - ≥100 kg: 10 mg daily
  - <100 kg but ≥50 kg: 7.5 mg daily
  - <50 kg: 5 mg daily

Therapeutic dose adjusted per NYP Infonet protocols.

7.7.1 Dosing Delays/Dose Modifications

Dose will be modified according to creatinine clearance; see Section 7.7 for further details.

Dose will be delayed or stopped if clinically significant major or non-major bleeding occurs.

7.8 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

Subjects enrolled on this study are permitted to receive other agents for treatment of their COVID-19 disease, including, but not limited to, remdesevir, eculizumab, tocilizumab, anakinra, and hydroxychloroquine. Co-enrollment on investigational trials for the treatment of COVID-19 is permitted.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment may continue for 28 days or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

In the event of hospital discharge, the decision to continue or discontinue anticoagulation therapy will follow institutional guidelines regarding anticoagulation at the time of hospital discharge (Appendix C). Anticoagulation treatment may continue beyond Day 28 if the investigator and/or treating physician considers it appropriate for the patient's clinical care.

Subjects may discontinue therapy if any of the following events occur:

- Major bleeding, defined (as per ISTH guidelines) as acute clinically overt bleeding associated with one or more of the following:
    - A decrease in hemoglobin of 2 g/dL or more;
    - A transfusion of 2 or more units of packed red blood cells;
    - Bleeding that occurs in at least one of the following critical sites:
        - Intracranial
        - Intra-spinal
        - Intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed)
        - Pericardial
        - Intra-articular
        - Intramuscular with compartment syndrome
        - Retroperitoneal
    - Bleeding that necessitates surgical intervention
- Clinically relevant non-major bleeding event defined as acute clinically overt bleeding that does not meet the criteria for major and consists of:
    - Any bleeding compromising hemodynamics;
    - Spontaneous hematoma larger than 25 cm2, or 100 cm2 if there was a traumatic cause;
    - Intramuscular hematoma documented by ultrasonography
    - Epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes
    - Hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention;
    - Clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding

7.10 Duration of Follow Up

Subjects will be followed for 6 months after discharge from hospital with the intention to get complete follow-up, or a minimum of vital status and the occurrence of recurrent deep venous thrombosis, pulmonary embolism, or major bleeding.

7.11 Measures to Minimize Bias: Randomization

Blocked randomization will be performed in the study. A series of blocks with random block sizes will be generated with a 1:1 allocation ratio to allow for an equal number of

patients in the intermediate dose prophylaxis arm and therapeutic anticoagulation treatment arm. Patients will not be stratified. The block randomization scheme will be provided by a biostatistician not directly involved in the analysis of the study and uploaded to the REDCap randomization module. Randomized assignments will be generated in REDCap after all eligibility criteria have been met. Blinding is not relevant as the study is open-label.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for study discontinuation
- Adverse events
- Concomitant medications
- Relevant medical history, including:
    - Major and clinically relevant non-major bleeding events
    - Objectively documented pulmonary embolism (PE)
    - Objectively documented and confirmed proximal deep vein thrombosis (DVT) of the upper or lower extremities
    - Objectively documented micro-thrombosis (skin biopsy)
    - Objectively documented thrombosis of the dialysis, continuous renal replacement (CRRT) filters
    - Objectively documented arterial thrombosis (stroke, myocardial infarction, limb ischemia)

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

9. Correlative/Special Studies

For subjects who agree to participate in a research repository, we will collect 5mL of plasma for thrombin generation assays and clot lysis at certain time points (see Section 6.1 for more details). Samples will be stored in a special freezer located in Dr. Laurence's laboratory.

10. Measurement of Effect

10.1 Response Criteria

1. Primary objective: To determine if therapeutic anticoagulation improves 30-day mortality in COVID 19 positive patients compared to intermediate dose prophylaxis.

2. Secondary Objectives

1. To assess if therapeutic anticoagulation reduced the length of ICU stay.
2. To determine if therapeutic anticoagulation reduces the number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction other) and micro thrombosis.
3. To evaluate if therapeutic anticoagulation leads to increase major and clinically relevant non-major bleeding events as defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria.

10.2 Duration of Response

Duration of response will be evaluated according to evidence of thrombosis or bleeding events during the follow up period as defined in 10.1

10.3 Progression-Free Survival

Not applicable.

10.4 Other Response Parameters

Normalization of laboratory values including: D-dimer, prothrombin time (PT), fibrinogen, FVIII and VWF and complete blood count

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

The blocked randomization scheme will be incorporated into REDCap and assignments will be generated via a randomization module within REDCap.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the

amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document. Given the disease state, potential participants may be sedated and/or on a ventilator; in such cases, the subject's legally authorized representative will be asked to provide informed consent on behalf of the subject. Subjects who enter the study with a legally authorized representative will be re-consented once they regain capacity to consent. Subjects who do not speak English may be consented using a translated short form in accordance with IRB requirements.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints:

Primary Endpoint:

Efficacy Outcomes

- Death at 30 days

Secondary Endpoints:

Efficacy Outcomes

1. Length of ICU stay
2. Objectively documented pulmonary embolism (PE), proximal deep vein thrombosis (DVT) of the upper or lower extremities, thrombosis of the dialysis, continuous renal replacement (CRRT) filters; micro-thrombosis (skin biopsy), arterial thrombosis (stroke, myocardial infarction, limb ischemia)
3. Major bleeding, (as per ISTH guidelines), and clinically relevant non-major bleeding events.

12.1.1 Primary Endpoint: Death at 30 days (primary)

12.1.2 Secondary Endpoint: Length of ICU stay.

12.1.3 Secondary Endpoint: Compositive endpoint of:

- Objectively documented pulmonary embolism
- Objectively documented confirmed proximal deep vein thrombosis (DVT) of the upper or lower extremities.
- Objectively documented micro-thrombosis (skin biopsy).
- Objectively documented thrombosis of the dialysis, continuous renal replacement (CRRT) filters.
- Objectively documented arterial thrombosis (stroke, myocardial infarction, limb ischemia).

12.1.4 Secondary Endpoint: <u>Safety Outcomes of major bleeding and clinically relevant non-major bleeding events defined as:</u>

Major bleeding, defined (as per ISTH guidelines) as acute clinically overt bleeding associated with one or more of the following:

A decrease in hemoglobin of 2 g/dL or more;
A transfusion of 2 or more units of packed red cells;
Bleeding that occurs in at least one of the following critical sites:

i. Intracranial
ii. Intra-spinal
iii. Intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed)
iv. Pericardial
v. Intra-articular
vi. Intramuscular with compartment syndrome
vii. Retroperitoneal

Bleeding that is fatal; Bleeding that necessitates surgical intervention.

Clinically relevant non-major bleeding event, defined as acute clinically overt bleeding that does not meet the criteria for major and consists of;

a) Any bleeding compromising hemodynamics;
b) Spontaneous hematoma larger than 25cm^2, or 100cm^2 if there was a traumatic cause;
c) Intramuscular hematoma documented by ultrasonography;
d) Epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes;
e) Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures;
f) Hemoptysis, hematemesis, or spontaneous rectal bleeding requiring endoscopy or other medical intervention;
g) Clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding;
h) Permanent early discontinuation of the anticoagulant due to safety reasons.

12.2 Sample Size/Accrual Rate

N=93 subjects per treatment arm (186 total). With approximately 93 patients in each treatment arm, a two-sample chi-square test with a 0.05 two-sided significance level will have 80% power to detect a difference in the 30-day mortality proportion between treatment arms of 12 % or greater. This calculation assumes a 30-day mortality proportion of approximately 15 % in the intermediate dose prophylaxis arm.

12.3 Stratification Factors

None

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

The chi-square test will be used to compare the proportion of patients who die by 30 days between the two treatment arms. A two-sided 95% confidence interval for the difference in the 30-day mortality proportion between the two arms will be calculated to assess the precision of the obtained estimate. All other efficacy outcome proportions and safety outcome proportions will be compared between the two treatment arms by the chi-square test or Fisher's exact test, as appropriate. Two-sided exact Clopper-Pearson 95% confidence intervals will be calculated for treatment arm differences, as appropriate. Participants who are discharged prior to day 30 for whom vital status cannot be assessed will be censored from the analysis. We expect this to occur only rarely.

12.4.2 Analysis of Secondary Endpoints

Length of ICU stay: We will compare the length of stay between arms using student's t-test. The length of time will be the total length of time in the ICU during the 30 days. This can be continuous or non-continuous time (i.e. a subject is discharged from ICU and then readmitted to ICU).

Thrombosis composite endpoint: All participants will be categorized as having developed one of the components of the composite endpoint or not through 30 days. The endpoint will be analyzed using chi-square test as described for the primary endpoint. We will also graphically display time to event. We will report the proportion of subjects in each diagnosed with each of these components. The primary analysis will censor participants who die without known thrombotic event. A supporting analysis will consider these deaths as part of the endpoint.

Safety Outcomes: All participants will be categorized as having developed a major bleeding events or a non-major clinically significant bleeding event and we will compare the proportions using chi-square test as described for the primary endpoint. We will also report major and non-major clinically significant bleeding event separately by arm.

Note: All secondary endpoint outcome proportions will be compared between the two treatment arms by the chi-square test or Fisher's exact test, as appropriate. Two-sided exact Clopper-Pearson 95% confidence intervals will be calculated for treatment arm differences, as appropriate.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for all parameters of interest will be calculated to assess the precision of the obtained estimates. All analyses will be performed in R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Note: The statistical considerations section was written in conjunction with the Division of Biostatistics, Department of Population Health Sciences.

12.5 Interim Analysis

We will be perform an interim analysis at one month from the initiation of the study

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment in either treatment arm. Two-sided exact Clopper-Pearson 95% confidence intervals will calculated for all toxicity proportions to assess the precision of the obtained estimates.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment according to the intention to treat (ITT).

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, computed tomography (CT), electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Because this is a trial focusing on a critically ill population where adverse events are expected to occur frequently, only AEs meeting the following criteria will be collected and reported:

1. AEs related to bleeding (any major or clinically significant non-major bleeding) or thrombotic events (DVT/PE, stroke, myocardial infarction, peripheral embolism, skin thrombosis).
2. Any adverse event that results in interruption or discontinuation of the assigned anticoagulant treatment.
3. Any adverse event that meets the criteria for serious, as defined in Section 13.2.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Expected adverse events for drugs administered as part of this protocol may be found in

the package inserts, located in Appendix A.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events described in section 13.1 will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Participants will be informed of any adverse event related to the anticoagulant treatment that represents a new or increased risk from participating in the study.

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

Not applicable.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of *xxxx* Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 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 during study visits and interviews of a study participant presenting for medical care, 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.

The study team will record 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. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

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.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO 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 UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

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

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

The Weill Cornell Medical College Data Safety Monitoring Board (DSMB) is being requested to review safety data and to make recommendations regarding continuation, termination, or modification to the study.

During the study, the DSMB will regularly (every 6 months) review all incidences of symptomatic DVT and PE, clinically relevant bleeding, and death, including those not yet adjudicated, which will result in recommendations to the study team.

An interim analysis will be performed one month after the first patient is enrolled.

16. References

1- Tang N et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020 epublished
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Appendix A

Package insert for each of the drugs used in this protocol is available at the links below:

Lovenox® (Enoxaparin sodium):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s085lbl.pdf

Sodium heparin (unfractionated heparin):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017029s140lbl.pdf

Argatroban Injection: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022485lbl.pdf

ARIXTRA® (fondaparinux sodium):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf

Appendix B

Table II. ISTH Diagnostic Scoring System for DIC.

Scoring system for overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: proceed

If no: do not use this algorithm

Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)

Score the test results

• Platelet count (>100 × 10^9/l = 0, <100 × 10^9/l = 1, <50 × 10^9/l = 2)

• Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)

• Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)

• Fibrinogen level (>1 g/l = 0, <1 g/l = 1)

Calculate score:

≥5 compatible with overt DIC: repeat score daily

<5 suggestive for non-overt DIC: repeat next 1–2 d

Source: Levi, M., Toh, C.H., Thachil, J. and Watson, H.G. (2009), Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Journal of Haematology, 145: 24-33. doi:10.1111/j.1365-2141.2009.07600.x

ASH COVID-19 Resources - Frequently Asked Questions:

COVID-19 and VTE-Anticoagulation
COVID-19 and Coagulopathy
COVID-19 and aPL Ab
COVID-19 and D-dimer
COVID-19 and Pulmonary Embolism

Appendix C

Weill Cornell Medicine/NewYork-Presbyterian: Discharge Thromboprophylaxis for Patients with COVID-19 Infection (April 20, 2020)