Protocol Outline

Protocol Title:	**Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19: A Cluster Based Randomized Selection Trial (IMPROVE-COVID)**
Protocol Version:	V2
Protocol Date:	12/30/20
Principal Investigator:	Sahil A. Parikh, MD
Biostatistics Core:	Shing Lee, PhD (Biostatistician) Cheng-Shiun Leu, PhD (Biostatistician)
Study Chairman:	Ajay J. Kirtane, MD, SM
Background and Significance /Preliminary Studies	Hemostatic, biomarker, and inflammatory changes are common in severe manifestations of coronavirus disease 2019 (COVID-19) (1-3). Such factors, as well as the bedridden status and critical illness may constitute a prothrombotic milieu, predisposing to venous and arterial thrombosis. However, the optimal antithrombotic regimen for patients with COVID-19, especially those with severe disease, remains uncertain and is currently an area of active clinical interest (4-6). Prophylactic-dose anticoagulation is generally recommended for acutely ill hospitalized patients. However, given the hemostatic abnormalities of severe COVID-19 illness, it is unknown whether more intensive anticoagulation is preferred to reduce the risk of thrombotic events, potentially mitigating microvascular and macrovascular thrombi and even disseminated intravascular coagulation (DIC). Further, the risks of therapeutic dose anticoagulation must be weighed against the bleeding risks inherent to this approach. To address this critical gap in knowledge in an area of clinical equipoise, we plan to conduct a cluster-randomized trial in patients admitted to a large volume academic medical center to select the best anticoagulation intervention.

Study Aims and Objectives	To assess the impact of intermediate-dose anticoagulation compared with prophylactic anticoagulation of critically ill patients with COVID-19 with regards to the composite primary endpoint of being alive and without clinically-relevant venous or arterial thrombotic events at discharge from the ICU (without transfer to palliative care unit/hospice) or at ICU duration (if ICU stay lasted 30 days or longer). Clinically relevant venous or arterial thrombotic events will all be adjudicated and are defined as any of the following: • Confirmed or treated deep venous thrombosis or pulmonary embolism • Type I myocardial infarction (MI) as confirmed by a combination of biomarkers, electrocardiogram and angiogram • New ischemic stroke • Acute limb ischemia • Actionable line thrombosis requiring escalation of anticoagulation or removal or replacement of the line • CVVH Filter thrombosis requiring escalation of anticoagulation • Other thrombotic events requiring anticoagulation (e.g., intracardiac thrombosis)
Secondary Aims:	1. To determine the impact of intermediate-dose anticoagulation compared with prophylactic anticoagulation on the individual components of the primary outcome in the ICU. 2. To determine the impact of intermediate-dose anticoagulation compared with prophylactic anticoagulation on ICU length of stay. 3. To determine the impact of intermediate-dose anticoagulation compared with prophylactic anticoagulation on rates of acute kidney injury and renal recovery in the ICU. 4. To determine the safety of intermediate-dose anticoagulation compared with prophylactic anticoagulation with respect to major bleeding (assessed by BARC criteria, also explored by ISTH and TIMI criteria) in the ICU. 5. To determine the impact of intermediate-dose anticoagulation compared with prophylactic anticoagulation on the individual components of the primary outcome until hospital discharge 6. To determine the impact of intermediate-dose anticoagulation compared with prophylactic anticoagulation on hospital length of stay.

Design	To avoid bias in statistical inference due to bias in sampling, only the first 60 patients will be included in this set of analysis. Details explain why bias occurs and how it will affect the statistical inference can also be found in the supplemental appendix. We will use the data from these 60 patients to generate the proportions of patients with the events specified as primary and secondary outcomes. We will also report the descriptive statistics (mean, median, interquartile range) for the time to ICU discharge. Graphical display of the data will be done as well. To compare the intervention effect between the two study groups on the primary and secondary outcomes, we will use generalized linear model with identity link function for continuous variables and logit link function for

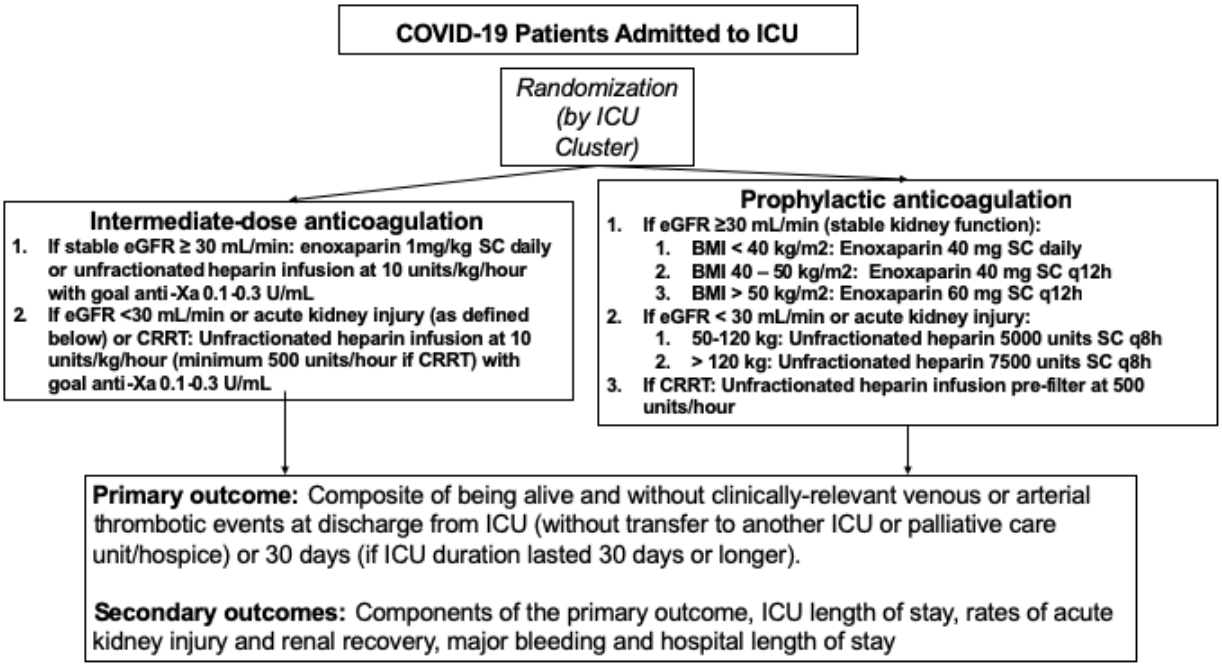
	dichotomous variables following the intent-to-treat principle. Covariates in these models include intervention group indicator, ICU indicators, and the potential confounding factors. The pre-spectified potential confounders are age, sex, weight, estimated glomerular filtration rate (eGFR), concomitant treatment with an IL-6 inhibitor, and concomitant treatment with corticosteroids. Generalized estimating equations methodology will be employed to account for the within-ICU correlation for subject assignment to the same ICU area. The key parameter of interest is the regression coefficient corresponding to the intervention group indicator which is the mean difference for continuous outcomes and log-odds ratio for dichotomous outcomes and it represents intervention effect of intermediate-dose anticoagulation compared with that of prophylactic anticoagulation. To report the trial findings, we will present the mean difference and odds ratio when appropriate and their corresponding p-values and 95% confidence intervals. Several pre-specified sensitivity analyses will be conducted: (1) excluding the patients who undergo CRRT during the study period; (2) excluding patients who experienced deviation in anticoagulation from randomized treatment arm; (3) analyzing the patients as the treatment they actually received. Additional sensitivity analysis will also be conducted to include covariates found imbalanced between the two intervention groups.
Intervention /Comparator	**Intervention arm: intermediate-dose anticoagulation** • If stable eGFR ≥ 30 mL/min: enoxaparin 1mg/kg SC daily or unfractionated heparin infusion at 10 units/kg/hour with goal anti-Xa 0.1-0.3 U/mL.[1] • If eGFR <30 mL/min or acute kidney injury (as defined below) or CRRT: Unfractionated heparin infusion at 10 units/kg/hour (minimum 500 units/hour if CRRT) with goal anti-Xa 0.1-0.3 U/mL.[2] **Control arm: prophylaxis** Prophylactic dose anticoagulation (per CUIMC Guidelines): • If eGFR ≥30 mL/min (stable kidney function): o BMI < 40 kg/m^2: Enoxaparin 40 mg SC daily o BMI 40 – 50 kg/m^2: Enoxaparin 40 mg SC q12h o BMI > 50 kg/m^2: Enoxaparin 60 mg SC q12h • If eGFR < 30 mL/min or acute kidney injury: o 50-120 kg: Unfractionated heparin 5000 units SC q8h o > 120 kg: Unfractionated heparin 7500 units SC q8h If CRRT: Unfractionated heparin infusion pre-filter at 500 units/hour

Primary Endpoint	Primary outcome: Composite of being alive and without clinically-relevant venous or arterial thrombotic events at discharge from ICU (without transfer to another palliative care unit/hospice) or at (if ICU duration lasted 30 days or longer). Clinically relevant venous or arterial thrombotic events will all be adjudicated and are defined as any of the following: • Confirmed or treated deep venous thrombosis or pulmonary embolism • Type I myocardial infarction (MI) as confirmed by a combination of biomarkers, electrocardiogram and angiogram • New ischemic stroke • Acute limb ischemia • Actionable line thrombosis requiring escalation of anticoagulation or removal or replacement of the line • CVVH Filter thrombosis requiring escalation of anticoagulation • Other thrombotic events requiring anticoagulation (e.g., intracardiac thrombosis)
Secondary Endpoints	1. Composite of being alive and without clinically-relevant venous or arterial thrombotic events at discharge from the hospital (without transfer to a palliative care unit/hospice) or at 30 days (if hospital stay lasted 30 days or longer) 2. Individual components of the primary outcome in the ICU 3. ICU length of stay 4. Need for renal replacement therapy 5. Major bleeding (assessed by BARC criteria, also explored by ISTH and TIMI criteria) 6. Individual components of the primary outcome during entire hospitalization. 7. Hospital length of stay
Estimated Sample Size	Up to 150 subjects (to be determined by sequential randomized selection design)

[1]This dose generally does not require routine monitoring of anti-Xa activity, but may be monitored by the primary team outside this study to assess for effectiveness and dose adjusted in consultation with pharmacist
[2]To be monitored at least 8 hours after the initiation of the infusion or any dose change.

Patients with improving kidney function or new AKI can be switched from one agent to the other within the same intervention group
Acute kidney injury defined as:

- Increase in SCr by ≥ 0.4 mg/dL within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <40 mL/h for 6 hours



I. Study Population

Patient Inclusion Criteria	• Age>18 years of age
	• Confirmed diagnosis of COVID-19 by RT-PCR
	• New admission to eligible CUIMC ICUs within 5 days
	  ○ Transfer from nonparticipating to participating ICU is eligible if otherwise meets eligibility criteria.
	  ○ Patients not on therapeutic anticoagulation and who were already admitted to participating ICU within 5 days of trial initiation are additionally eligible.

Patient Exclusion Criteria	• Weight under 50kg
	• Contraindication to anticoagulation in the opinion of the treating clinician including
	  ○ overt bleeding
	  ○ platelet count <50,000
	  ○ BARC major bleeding in the past 30 days
	  ○ GI bleeding within 3 months
	  ○ history of intracranial hemorrhage
	  ○ Ischemic stroke within the past 2 weeks
	  ○ craniotomy/major neurosurgery within the past 30 days
	  ○ cardiothoracic surgery within the past 30 days
	  ○ intra-abdominal surgery within 30 days prior to enrollment
	  ○ Head or spinal trauma in the last months
	  ○ History of uncorrected cerebral aneurysm or arteriovenous malformation AVM

	○ Intracranial malignancy ○ Presence of an epidural or spinal catheter ○ Recent major surgery within the last 14 days ○ Decrease in hemoglobin >3 g/dL over the last 24 hours ○ Allergic reaction to anticoagulants (e.g. Heparin Induced Thrombocytopenia) as documented in the electronic health records. Extracorporeal membrane oxygenation (ECMO) support or other mechanical circulatory support. • Severe chronic liver dysfunction (history of portosystemic HTN, esophageal varices, or Child-Pugh class C or above or similar MELD scores), abnormality in liver function tests (AST, ALT, bilirubin) 5 times greater than upper normal limit. • History of cirrhosis • A history of congenital bleeding diatheses or anatomical anomaly that predisposes to hemorrhage (e.g. hemophilia, hereditary hemorrhagic telangiectasia) • Treating physician preference for therapeutic anticoagulation • Enrollment in other concurrent trials related to anticoagulant or antiplatelet therapy • Existing treatment with therapeutic anticoagulation during the previous 7 days of hospitalization prior to ICU admission (e.g. for VTE, atrial fibrillation, mechanical valve, etc). • CMO orders prior to enrollment.

II. Study Procedures

a. Screening procedures
b. Randomization
c. Study intervention
d. Study Assessments and Activities

Screening procedures	All patients in participating CUIMC ICUs will be screened by the study team. Study eligibility criteria (described above) will be implemented to identify the modified intention-to-treat cohort.
Randomization procedures	Patients, when eligible, will be enrolled to the study at the “first-come-first-serve” basis. All the participating ICUs can have 2 possible “room type”: negative pressure rooms and non-negative pressure rooms. Each of the participating ICUs will be divided into either two or four clusters as follows. Any ICU with only one room type (i.e., it only has negative pressure rooms or only has non-negative pressure rooms) will be divided into 2 clusters. For ICUs that contain both room types (i.e., it has negative pressure rooms and non-negative pressure rooms), we will divide that ICU into 4 clusters with two clusters for each room type. Two clusters within each ICU and each room type will then be randomized to either of the study arms. . Enrolled patients will receive the treatment according to the cluster of ICU they are assigned. Post-randomization pairing scheme will be employed to form the pairs if the stopping criterion is not reached at the time that first 60 outcomes have been observed. As the hospital administration changed the room type to accommodate the decrease of COVID patients (e.g., some negative

	pressure rooms were changed to non-negative pressure rooms), we currently recruitment included more patients in the prophylactic dose group than those of the intermediate dose group. At the recommendation of the DSMB, in each ICU and each room type, we will randomize "intermediate dose rooms" and "prophylactic dose rooms" in a 3:1 ratio until we reach enrollment of 30 patients for one group and we will then only assign patients to the other group until we achieve the recruitment of 30 patients that group as well. After we recruit 30 patients for each arm, the ratio of the rooms will be changed back to 1:1 (intermediate vs. prophylactic) for the subsequent recruitment.
Study intervention	• Each cluster will be randomized to one of the two antithrombotic regimens: prophylactic-dose or intermediate dose as described above The choice of agents will be dependent upon the renal function (at the time of enrollment and every subsequent day). • At the onset of study enrollment, clusters including patients admitted within the past 5 days will be randomized. • Patients who meet eligibility by screening team will be enrolled.Patient is considered enrolled after a co-investigator has confirmed all inclusion/exclusion criteria have been met. Assessment of appropriateness of anticoagulation dose will occur daily based on the renal function, progressive thrombocytopenia or anemia, or development of another indication for anticoagulation such as new-onset atrial fibrillation, • Patients' treatment course will be followed from randomization to hospital discharge or 30 days, whichever happens earlier. • Patients will continue with randomization therapy until discharged from the ICU, except in the setting of an adverse event attributed to anticoagulation, developing an event requiring therapeutic anticoagulation, or change in code status to comfort measures. • Patients transferred between participating ICUs will remain in the treatment arm assigned at initial randomization. Recommendation will be to continue study treatment if patient transferred to ICUs not participating in the present trial. If the study treatment is changed by the primary treating team in the second ICU, then patient will be evaluated by intention to treat principle. **Intervention arm: intermediate-dose anticoagulation** • If stable eGFR ≥ 30 mL/min: enoxaparin 1mg/kg SC daily[1] • If eGFR <30 mL/min or acute kidney injury (as defined below) or CRRT: Unfractionated heparin infusion at 10 units/kg/hour (minimum 500 units/hour if CRRT) with goal anti-Xa 0.1-0.3 U/mL[2] **Control arm: Prophylactic dose anticoagulation** (per CUIMC Guidelines): • If eGFR ≥30 mL/min (stable kidney function): o BMI < 40 kg/m^2: Enoxaparin 40 mg SC daily o BMI 40 – 50 kg/m^2: Enoxaparin 40 mg SC q12h o BMI > 50 kg/m^2: Enoxaparin 60 mg SC q12h • If eGFR < 30 mL/min or acute kidney injury: • If eGFR < 30 mL/min or acute kidney injury:

	○ 50-120 kg: Unfractionated heparin 5000 units SC q8h ○ > 120 kg: Unfractionated heparin 7500 units SC q8h • If CRRT: Unfractionated heparin infusion pre-filter at 500 units/hour
Study assessment and activities	All anticoagulation medications are standard of care according to discussions between clinician leadership in multiple disciplines and review of treatment protocols from institutions in the region and internationally. Anticoagulants will be ordered through the hospital pharmacy. Patient receiving any anticoagulation are at risk for development of hemorrhage, thrombocytopenia, and in rare cases (overall rate of 0.2%) heparin induced thrombocytopenia (7). Patients who have a bleeding event may have cessation of the administered drug per clinical standard of care, and in some cases may require transfusion of blood products, and additional testing and therapy to identify and treat the source of bleeding. Patients who develop a thrombotic event may have intensification of anticoagulation per clinical standard of care. We will collect all clinical, laboratory and imaging data generated per standard of care throughout the patient's hospitalization. Primary and Secondary endpoints will be assessed at ICU discharge, hospital discharge and 30 days if the patient is still hospitalized.

III. Endpoint Definition

a) **Endpoint Reporting Requirements**

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation and will continue until the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation.
Endpoint data will be collected throughout the time period defined above and will be entered on a CRF.

For the purposes of this investigation the following are reportable endpoints:

Death	
Deep venous thrombosis	Diagnosed on duplex ultrasonography including upper (internal jugular, subclavian, axillary/brachial) and lower extremity (iliac, femoral/popliteal, gastrocnemius, peroneal, posterior tibial) thrombosis
Pulmonary embolism	Diagnosed on CT angiography, V/Q scan, or invasive pulmonary angiography
Type I myocardial infarction	Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:: symptoms of ischemia, new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB); development of

	pathological Q waves on the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus by angiography or autopsy
Ischemic stroke	Neurological dysfunction caused by focal cerebral, spinal, or retinal infarction based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. Exclude hemorrhagic infarction.
Acute limb ischemia	Sudden decrease in limb perfusion that threatens limb viability with confirmed arterial obstruction based on duplex ultrasonography or invasive peripheral angiography
Actionable line thrombosis	Arterial or central venous catheter thrombosis that results in removal or replacement of catheter or initiation of therapeutic anticoagulation. Excludes use of indwelling tPA.
CVVH filter thrombosis	Filter thrombosis requiring exchange in order to resume continuous veno-venous hemofiltration (CVVH) or resulting in cessation of CVVH
Other thrombotic events requiring anticoagulation	For example atrial fibrillation, left ventricular thrombus, right ventricular thrombus, etc.
Acute kidney injury	KDIGO criteria: 1. Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or 2. Increase in sCr ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or 3. Urine volume <0.5 mL/kg/h for 6 hours.
Serious bleeding	• BARC 3 or 5 bleeding (3: decrease in the hemoglobin of >3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; 5: fatal)

	• ISTH major bleeding: 1: Fatal bleeding, and/or 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or 3. Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. • TIMI major bleeding: Any intracranial bleeding (excluding microhemorrhages ≤10 mm evident only on gradient-echo MRI), or Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL, or Fatal bleeding (bleeding that directly results in death within 7 d

IV. Event Adjudication

A clinical events committee will be formed for adjudication of clinical endpoints. Suspected components of the primary endpoint as well as the secondary endpoints, including the bleeding endpoint as documented in case report forms will be adjudicated based on pre-defined clinical definitions of venous thromboembolism, myocardial infarction, ischemic stroke, acute limb ischemia, clinically-actionable line thrombosis, and major bleeding. All suspected events will be independently reviewed by two physicians blinded to randomized group assignment. If there is disagreement on whether an endpoint event has occurred, the case will be reviewed by the clinical events committee for adjudication.

V. Safety Monitoring Plan

All events outlined above will be reported to the Clincial Events Committee (CEC) and Data and Safety Monitoring Board (DSMB) and reviewed on a regular basis. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend to the Study Chairman to stop or otherwise modify the study. The Study Chairman will make the final decision after weighing the recommendation of the DSMB whether the study should then be stopped, modified or continued without change. The DSMB procedures will be described in the DSMB Charter.

VI. Risk/Benefit Analysis

Include research related risks and potential benefits (if any).

There is equipoise for the antithrombotic treatment intensity in patients with severe COVID-19. The table below summarizes the potential benefits and risks of intermediate-dose vs. prophylactic dose anticoagulation.

Potential benefits of intermediate-dose vs. prophylactic dose anticoagulation	• Potential for reduced risk of thrombotic complications (including VTE, MI, stroke, and line thrombosis) • Potential for improving the recovery from need from mechanical ventilation. • Potential for reducing the risk of DIC. • Potential for reducing the risk of renal failure. • Potential for reducing mortality as a result of reducing the above components.
Potential risks of intermediate-dose vs. prophylactic dose anticoagulation	• Increased risk of bleeding, including major bleeding • Heparin induced thrombocytopenia

VIII. Study Design and Analysis Plan (include timing and primary and secondary endpoint analysis)

In order to assess event rates and appropriately adjust study measures as part of adaptive trial design, a blinded interim analysis at the combined event rate of both study arms will be performed. Once the trial is completed, analysis will be performed by intention to treat.

General Design

This is a cluster randomized-controlled clinical selection trial of interventions for anticoagulation for COVID-19 patients in the ICU. ICU subunits will be randomly assigned to give patients intermediate (higher) dose or prophylactic (lower) dose of anticoagulation. The primary goal of the trial is *to select the best intervention* with a high probability of *correct* selection if one intervention is truly superior by a pre-specified effect size. Up to 100 patients (with expected sample sizes between 69-75 patients for the most likely scenarios) will be enrolled in the study, using a novel sequential design. Each time an outcome is observed for a patient, those outcomes are added to a running tally of successes for each intervention. There is a pre-specified criterion in terms of the success tallies for selecting arm as evidence of apparent superiority accumulates. With this sequential procedure, the preferred intervention can be selected during the ongoing enrollment as soon as the pre-specified selection criteria are met, and further enrollment will cease. To ensure that there will be some unbiased estimates of the proportion of patients with a good outcome available for each intervention arm, the selection criteria will not be applied until 60 patients have been observed. This novel approach based on the Levin-Robbins-Leu family of sequential selection procedures [18-23].

Study Implementation

The identification of a preferred treatment will be done using an innovative sequential selection procedure, which will substantially reduce the number of patients in comparison to a hypothesis test procedure. The data will be examined each time a pair of patients completes follow-up after 60 patients have been observed.

The goal of the procedure is to make a correct selection with high probability. The procedure follows the preference zone / indifference zone approach, wherein we require the selection procedure to guarantee a probability of at least 90% *correct* selection (of the truly best intervention), assuming that one is truly superior to the other by a pre-specified amount. This pre-specification defines a region in the parameter space called the *preference zone*. If the best intervention does not exceed the next best by the pre-specified amount, the success probabilities are said to lie in the *indifference zone*, where we shall be indifferent to the fact that the probability of correct selection may be less than 90%. For this trial, the preference zone consists of all parameter vectors (p_1, p_2) of success probabilities where the odds ratio comparing the largest to the next largest is greater than or equal to 2.15 (p_1=0.35, p_2=0.20).

The selection procedure is specified by the sampling rule, the stopping rule, and the terminal decision rule, as follows.

Sampling rule: Patients, when eligible, will be enrolled to the study at the “first-come-first-serve” basis. All the participating ICUs can have 2 possible “room type”: negative pressure rooms and non-negative pressure rooms. Each of the participating ICUs will be divided into either two or four clusters as follows. Any ICU with only one room type (i.e., it only has negative pressure rooms or only has non-negative pressure rooms) will be divided into 2 clusters. For ICUs that contain both room types (i.e., it has negative pressure rooms and non-negative pressure rooms), we will divide that ICU into 4 clusters with two clusters for each room type. Two clusters within each ICU and each room type will then be randomized to either of the study arms. . Enrolled patients will receive

the treatment according to the cluster of ICU they are assigned. Post-randomization pairing scheme will be employed to form the pairs if the stopping criterion is not reached at the time that first 60 outcomes have been observed. As the hospital administration changed the room type to accommodate the decrease of COVID patients (e.g., some negative pressure rooms were changed to non-negative pressure rooms), we currently recruitment included more patients in the prophylactic dose group than those of the intermediate dose group. Pending the approval of DSMB, in each ICU and each room type, we will randomize "intermediate dose rooms" and "prophylactic dose rooms" in a 3:1 ratio until we reach enrollment of 30 patients for one group and we will then only assign patients to the other group until we achieve the recruitment of 30 patients that group as well. After we recruit 30 patients for each arm, the ratio of the rooms will be changed back to 1:1 (intermediate vs. prophylactic) for the subsequent recruitment.

Success tallies:
Each time the follow-up for each patient in a pair is complete and a "good" or "poor" outcome is determined for each based on the composite primary outcome, the pair becomes "observed" and is available for sequential monitoring by adding to a running tally of the "good" outcomes for each intervention. These *success tallies* are used for the stopping rule.

Stopping and Decision rule: The criterion for stopping is a *difference of 4 or more between the tallies*if this occurs at or before 60 patients' outcomes have been observed. At that time, intervention with the largest success tally is selected as the preferred intervention. However, we will not stop the procedure and make a decision before the outcomes of the first 60 patients have become available. In addition, if the criterion for stopping has not been reached at or before 100 outcomes have been observed, the trial will stop by *truncation* with a maximum of 100 patients. At that time, intervention with the largest success tally is selected as the preferred intervention. If there are ties for the largest success tally at time of truncation, we will select the intervention according to other considerations (safety, better secondary outcomes, etc.).

Incomplete pairs:
If at the time of stopping there are partially filled or partially observed pairs of patients that have been randomized and have started their intervention, we will allow each patient in each such pair to complete their follow-up even if the arm to which they were randomized is eliminated.

Operating characteristics: In Appendix, we calculate the operating characteristics for various scenarios via simulation study with 100,000 replications. Operating characteristics include the probability of correction, the expected total number of patients, the expected total number of patients with bad outcome, the probability that the trial will be truncated before reaching the criterion for stopping, the probability of reaching a decision after exactly 60 patients (30 in each arm), the probability of correct selection after exactly 60 patients (30 in each arm), and the conditional probability that correct selection is made given that exactly 60 patients (30 in each arm). Scenarios discussed cover the parameters in the preference zone, in the indifference zone, and the null case (i.e., $p_1=p_2$).

Analysis of the Primary Endpoint with the Full Sample
In general, a selection procedure, unlike a hypothesis test procedure, is not specifically designed to provide a *p*-value below a conventional level of significance. Indeed, we will *not* be declaring any differences statistically significant, as that is explicitly *not* the goal of the present selection trial, i.e., we are explicitly *not interested* in testing the null hypothesis of no differences between the interventions. Instead, because the adaptive sequential selection procedure can be described as a procedure that samples until there is a pre-specified *weight of evidence* for making correct selections, assuming there is a minimum true degree of superiority as measured by the design odds

ratio, we will quote the *likelihood ratio (LR) measure of weight of evidence* in various ways. Details regarding how the LR was calculated and examples to illustrate their interpretations can be found in the supplemental appendix.

Endpoint Evaluation
All patients will be evaluable for ischemic outcomes and bleeding from the time of their first treatment with the anticoagulant.

Analysis of Primary Endpoint and Secondary Endpoints for the first 60 patients
To avoid bias in statistical inference due to bias in sampling, *only* the first 60 patients will be included in this set of analysis. Details explain why bias occurs and how it will affect the statistical inference can also be found in the supplemental appendix. We will use the data from these 60 patients to generate the proportions of patients with the events specified as primary and secondary outcomes. We will also report the descriptive statistics (mean, median, interquartile range) for the time to ICU discharge. Graphical display of the data will be done as well. To compare the intervention effect between the two study groups on the primary and secondary outcomes, we will use generalized linear model with identity link function for continuous variables and logit link function for dichotomous variables following the intent-to-treat principle. Covariates in these models include intervention group indicator, ICU indicators, and the potential confounding factors. The pre-spectified potential confounders are age, sex, weight, estimated glomerular filtration rate (eGFR), concomitant treatment with an IL-6 inhibitor, and concomitant treatment with corticosteroids. Generalized estimating equations methodology will be employed to account for the within-ICU correlation for subject assignment to the same ICU area. The key parameter of interest is the regression coefficient corresponding to the intervention group indicator which is the mean difference for continuous outcomes and log-odds ratio for dichotomous outcomes and it represents intervention effect of intermediate-dose anticoagulation compared with that of prophylactic anticoagulation. To report the trial findings, we will present the mean difference and odds ratio when appropriate and their corresponding p-values and 95% confidence intervals. Several pre-specified sensitivity analyses will be conducted: (1) excluding the patients who undergo CRRT during the study period; (2) excluding patients who experienced deviation in anticoagulation from randomized treatment arm; (3) analyzing the patients as the treatment they actually received. Additional sensitivity analysis will also be conducted to include covariates found imbalanced between the two intervention groups.

Operating characteristics of the Study Design
The stopping criterion of a lead of at least 4 between largest and smallest success tallies was chosen to achieve a probability of correct selection of at least 90% for any true success probabilities lying in the preference zone characterized by an odds ratio of 2.15 or greater between the true success probabilities of the two interventions. For example, true success probabilities of 0.35 and 0.20 with an odds ratio of 2.15 is lying on the boundary between the preference and indifference zones. For any such configuration with $\{p_1/(1-p_1)\}/\{p_2/(1-p_2)\} = 2.15$, the selection procedure will result in a correct selection with at least 90% probability. Table 1 shows the operating characteristics of the selection procedure under various scenarios of true success probability configurations for the two arms.

TABLE 1
Operating characteristics of the selection procedure

Scenario 1. p_1=0.35, p_2=0.20, criterion for stopping is a difference of 4 between the tallies, truncation at 100 patients, minimum # of patients before possible selection=60						
ET	EF	PCS	P[truncation]	P[T=T_0]	P[T=T_0,CS]	P[CS|T=T_0]
68.4	49.6	95.1%	10.2%	62.6%	61.6%	98.4%
Scenario 2. p_1=0.30, p_2=0.20, criterion for stopping is a difference of 4 between the tallies, truncation at 100 patients, minimum # of patients before possible selection=60						
ET	EF	PCS	P[truncation]	P[T=T_0]	P[T=T_0,CS]	P[CS|T=T_0]
74.0	55.5.4	87.1%	21.5%	46.6%	44.0%	94.5%
Scenario 3. p_1=0.20, p_2=0.20, criterion for stopping is a difference of 4 between the tallies, truncation at 100 patients, minimum # of patients before possible selection=60						
ET	EF	PCS	P[truncation]	P[T=T_0]	P[T=T_0,CS]	P[CS|T=T_0]
83.0	66.4	50.2%	43.5%	25.7%	12.9%	50.2%

ET is the expected total number of patients
EF is the expected total number of patients with bad outcome
PCS is the probability of correct selection
P[truncation] is the probability that the trial will be truncated before reaching the criterion for stopping
P[T=T_0] is the probability of reaching a decision after exactly 60 patients (30 in each arm)
P[T=T_0, CS] is the probability of correct selection after exactly 60 patients (30 in each arm)
P[CS|T=T_0] is the conditional probability that correct selection is made given that exactly 60 patients (30 in each arm)

The first scenario corresponds to the abovementioned design alternative which we believe is minimal clinically meaningful and worthwhile. The second scenario describe the operating characteristics of the selection procedure inside the indifference zone, assuming smaller differences in the success rates for the two interventions. The third scenario illustrates a case where there is no true difference in the rates for the two arms.

In scenarios 1 and 2 where there is a superior arm, the design chooses the superior arm over 87% of the time across these scenarios with average sample sizes between 68.4 and 74.0. Under the design alternative, there is 82.5% probability that we will stop the trial with 30 patients per arm. The probability of having to truncate the study ranges from 3.5% to 10.6%, with the lowest probability for our design alternative. The probability of selecting the superior arm at exactly 100 patients are enrolled is between 63.7% and 81.9% in these scenarios, which explains the need to continue enrollment to ensure that the correct dose is selected with high probability. Nevertheless, the conditional probability that correct selection is made given that exactly 100 patients have been randomized is very high (between 96.4% and 99.2%).

In scenario 3, there is no difference between the two arms. Thus, the design randomly selects one of them with a probability of 0.50. However, given that they are all the same, it is acceptable to select any of them and thus the probability of selecting an acceptable intervention is 100%. Because there is no superior intervention in this scenario, evidence of an apparent advantage accumulates more slowly than under other scenarios and thus the procedure incurs a larger average sample size and probability of truncation.

Formula to Calculate the Likelihood Ratio and its Interpretations

At the end of the trial, we will calculate the likelihood of the success tallies. This likelihood is given by

$$L(p_i, p_j \mid X_i^{(n)}, X_j^{(n)}) = p_i^{X_i^{(n)}} (1-p_i)^{n-X_i^{(n)}} \; p_j^{X_j^{(n)}} (1-p_j)^{n-X_j^{(n)}},$$

where $X_i^{(n)}$ and $X_j^{(n)}$ are the observed success tallies for the selected and not selected intervention and where p_i and p_j are the respective true success probabilities. We will also calculate the likelihood of the observed success tallies under the assumption that we erred in our selection and that the true success probabilities are those for the two interventions *transposed*, namely, $L(p_j, p_i \mid X_i^{(n)}, X_j^{(n)})$. The *likelihood ratio LR* is the ratio of these two likelihoods. It can be shown that *LR*, equals the true odds ratio raised to the fourth power,

$$LR = \frac{L(p_i, p_j \mid X_i^{(n)}, X_j^{(n)})}{L(p_j, p_i \mid X_i^{(n)}, X_j^{(n)})} = \left\{ \frac{p_i/(1-p_i)}{p_j/(1-p_j)} \right\}^4,$$

in the case where the trial ends meeting the selection criterion. In the case of truncation, the exponent 4 is replaced by $X_i^{(n)} - X_j^{(n)}$. We will evaluate *LR* at the maximum likelihood estimates of p_i and p_j, which are the adjusted sample proportions $(X_i^{(n)} + 0.5)/(n+1)$ and $(X_j^{(n)} + 0.5)/(n+1)$. The values of success tallies used in *LR* are those used in the selection criteria, i.e., without data from incomplete pairs. However, for the values of p_i and p_j used in *LR*, we will use the corresponding sample proportions using *all* of the available outcome data including data from incomplete pairs. The *LR* may offer strong evidence of correct selection (if *LR*>10) or only weak evidence, and the *LR* weight of evidence will be taken account of in evaluating whether or not to mount a subsequent phase 3 trial.

For instance, suppose we stop after 60 patients. If the difference between the two groups' success tallies is exactly equal to 4 (the minimum given the design), the likelihood ratio (LR) in favor of having selected the truly better treatment as opposed to having made a mistaken selection equals the odds ratio (OR) raised to the 4th power. Thus, at the design alternative p_1=0.35, p_2=0.20, the LR would be 21.5. This is usually considered "very strong" evidence. Likelihood ratios in excess of 8 or 10 are generally considered to be moderate to strong evidence [Royall R. Statistical Evidence: A likelihood paradigm. 1997 Chapman and Hall/CRC]. For comparison, the usual "significant at p<0.05" corresponds to a LR of only 6.8 in large samples. Furthermore, if the design alternative holds, it is highly probable the difference between success tallies will be greater than 4. For example, if the tallies are 11 (about 30×0.35) and 6 (=30×0.20), the LR under the design alternative is much larger (46), very strong evidence in favor of a correct selection.

To address the weight of evidence in favor of the maximum likelihood estimate (*mle*) being the true parameters as opposed to the *null* hypothesis p_1=p_2 being the true parameters, the generalized LR is 11.2 for the case *T*=60, X_1=20, X_2=10, which would again be moderate to strong evidence. On the other hand, if X_1=14, X_2=10, LR=1.55, very weak evidence against the null hypothesis. Assuming the trial does not stop at *T*=60, the above LR's will be assessed with the data at the time of selection at the observed *mle*'s for weight of evidence in favor of correct selection and for weight of evidence against the null hypothesis. The assessments will be repeated when all data have been observed, including overrun data coming in after the time of selection.

Minimizing Selection Bias

While the primary aim for the study is to select the best intervention from the 2 candidates, we are also interested in conducting point estimation and hypothesis test for the primary and secondary outcomes when appropriate and to conduct such analysis, *only* the first 30 pairs of patients can be included. This is because we will *not* enroll any additional patients if decision can be made based on the data from the first 30 pair of patients. In other words, the enrollment of 31st pair of patients and thereafter will not be necessary *unless* we don't have sufficient evidence (i.e., the difference in number of "good" outcomes is less than 4) to demonstrate one intervention is better than the other from the outcomes obtained from the first 30 pairs. Therefore, when we have to continue sampling (after the first 30 pairs) until a winner appears and use the entire sample to construct the analysis, two consequences will occur: (1) from point estimation standpoint, the probability of "good" outcome for the winner will be over-estimated (and for the loser will be under-estimated); and (2) from hypothesis testing standpoint, as sampling plan "enforces" the data to support the alternative hypothesis, bias then introduced against the null.

Nevertheless, to prevent any bias due to sampling, we propose to recruit the first 30 pairs without any look and/or comparison of their primary and secondary efficacy outcomes (unless the early stopping is required from the recommendation of DSMB due to safety concern). In such case, the recruitment of first 30 pairs of patients is independent of their outcome as we usually do for any fixed sample size design. Thus, conducting point estimation (together with a 95% confidence interval) and hypothesis testing with those 60 patients is entirely appropriate (i.e., can be done unbiasedly).

VII. References

1. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019 (COVID-19): a pooled analysis. Thromb Haemost In press.
2. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020.
3. Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020.
4. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020.
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020.
6. Crackower MA, Sarao R, Oudit GY et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002;417:822-8.
7. Smythe MA, Koerber JM, Mattson JC. The incidence of recognized heparin-induced thrombocytopenia in a large, tertiary care teaching hospital. Chest 2007;131:1644-9.