A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19

Short Title: ACTIV-4 ACUTE (AC-INPT)

ClinicalTrials.gov Number: NCT04505774

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Version Number: 1.1

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Protocol Revision History:

<table>
<thead>
<tr>
<th>Version Number</th>
<th>Status/Summary of Revisions Made</th>
<th>Version Date</th>
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</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Appendix 1 outlined possible example scenarios for adaptive design, Arms A and B included.</td>
<td>August 21, 2020</td>
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</table>
| 1.1            | • Section 5.1 Inclusion Criteria: Broadened type of SARSCoV2 tests, in accordance with NIH recommendations  
• Appendix 1: Revised to reflect the master protocol current state of arms  
• Appendix 1.1: Adds arm C  
• Appendix 1.2: Adds arm D  
• Appendix 2: Neuroimaging detailed criteria for hemorrhagic stroke conversion removed to be refined in the event charter  
• Appendix 2: The method of calculation of ventilator-free days was removed from the description of the primary endpoint, where it is not relevant. The definition will appear in a manual.  
• Appendices 1 and 3: New exclusion for Arm A for patients who require ICU level of care at screening, based on DSMB review and NHLBI Determination, as of Dec 19, 2020  
• New exclusion for Arm B for patients who do not require ICU level of care at screening, based on DSMB review and NHLBI Determination, as of Jan 21, 2021  
• Appendix 3: Added recommendation to enroll patients with elevated d-dimer  
• Appendices 3, 4: Clarified quality of life assessment on schedule of assessments  
• Appendix 5: Clarification on blood collection window  
• Appendix 7 Added for arm C  
• Section 13.3.2: Added investigator “designee” to consent process  
• Appendix 8: Added for arm D | February 01, 2021 |
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IND Waiver  
ClinicalTrials.gov Identifier NCT04505774  
WIRB study number 20202415 |
Statement of Compliance

In the United States this study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation (“ICH”) Guideline for Good Clinical Practice (“GCP”) (sometimes referred to as “ICH-GCP” or “E6”) and the General Data Protection Regulations (GDPR) will be applied only to the extent that it is compatible with FDA and DHHS regulations.

Outside of the United States this study will be conducted according to local legal and regulatory requirements and regulations, ICH guidelines, and GDPR guidelines as applicable.

The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations (if applicable), and ICH E6(R2) GCP guidelines.

Version Date: Feb 01.2021

________________________________________________________________________
Signature of Principal Investigator Date

________________________________________________________________________
Printed Name of Principal Investigator

________________________________________________________________________
Name of Facility

________________________________________________________________________
Location of Facility (City, Country)
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<th>Full Form</th>
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<tr>
<td>AE</td>
<td>Adverse Event/Adverse Experience</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome.</td>
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<td>AT</td>
<td>Arterial Thrombosis</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
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<tr>
<td>CrCl</td>
<td>Creatinine Clearance</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus Disease</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CSOC</td>
<td>Clinical Study Oversight Committee</td>
</tr>
<tr>
<td>DCC</td>
<td>Data Coordinating Center</td>
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<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
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<tr>
<td>DIC</td>
<td>Disseminated Intravascular Coagulation</td>
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<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal Membrane Oxygenation</td>
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<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FFR</td>
<td>Federal Financial Report</td>
</tr>
<tr>
<td>FWA</td>
<td>Federal Wide Assurance</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HFNO</td>
<td>High-flow Nasal Oxygen</td>
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<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>HIT</td>
<td>Heparin Induced Thrombocytopenia</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISM</td>
<td>Independent Safety Monitor</td>
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<tr>
<td>ISTH</td>
<td>International Society on Thrombosis and Haemostasis</td>
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<tr>
<td>ITT</td>
<td>Intent to Treat</td>
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<tr>
<td>IV</td>
<td>Invasive Ventilation</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
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<tr>
<td>KDIGO</td>
<td>Kidney Disease Improving Global Outcomes</td>
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<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>MOP</td>
<td>Manual of Procedures</td>
</tr>
<tr>
<td>N</td>
<td>Number (typically refers to participants)</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
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<tr>
<td>OHRP</td>
<td>Office for Human Research Protections</td>
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<td>OHSR</td>
<td>Office of Human Participants Research</td>
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<tr>
<td>OSFD</td>
<td>Organ Support Free Days</td>
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<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>PRBC</td>
<td>Packed Red Blood Cells</td>
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<tr>
<td>PTT</td>
<td>Partial Thromboplastin Time</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event/Serious Adverse Experience</td>
</tr>
<tr>
<td>sICH</td>
<td>Symptomatic Intracranial or Intracerebral Hemorrhage</td>
</tr>
<tr>
<td>SOC</td>
<td>Standard of Care</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
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<td>WHO</td>
<td>World Health Organization</td>
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# Master Protocol Summary

<table>
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<th>Title</th>
<th>A Multicenter, Adaptive, Randomized, Open Label Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19</th>
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<tbody>
<tr>
<td>Short Title</td>
<td>ACTIV-4 ACUTE</td>
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<tr>
<td>Brief Summary</td>
<td>This is a randomized, open label, adaptive platform trial to compare the effectiveness of antithrombotic strategies for prevention of adverse outcomes in COVID-19 positive inpatients</td>
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</table>
| Objectives | 1. To determine the most effective antithrombotic strategy for increasing the number of days free of organ support and reducing death. 
2. To determine the most effective antithrombotic strategy on the composite endpoint of death, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, or other systemic arterial thrombosis (AT). 
3. To assess the safety of antithrombotic strategies through the endpoint of major bleeding as defined by ISTH. 
4. To compare the effect of antithrombotic strategies on the endpoint of all-cause mortality in the study population. 

Assessment of efficacy and safety will yield information of the net clinical benefit of different antithrombotic strategies in the study population. It will also yield information on outcomes specific to underrepresented minority populations, specifically African- and Hispanic-descent persons. |
| Methodology | Adaptive Randomized Platform Trial |
| Endpoints | Primary Endpoint: 21 Day Organ Support Free Days, which is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry. Organ Support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support, with death at any time (including beyond 21 days) during the index hospitalization assigned -1 days. Key Secondary Endpoint: Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Other Secondary Endpoints: Composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Acute kidney injury defined by KDIGO criteria, Individual endpoints comprising the key secondary endpoint, death during hospitalization, 28 Day Ventilator-Free Days, 28 Day Vasopressor Free Days, 28 Day Renal Replacement Free Days, WHO clinical scale, 28 Day Hospital Free Days, 28 day organ support free days, and all-cause mortality at 90 days. Primary Safety Endpoint: Major bleeding (as defined by the ISTH) Secondary Safety Endpoint: Confirmed heparin induced thrombocytopenia (HIT) |
| Study Duration | Approximately 1 year |
| Participant Duration | Hospital duration with periodic contact at post-discharge, including at 90 days, with potential contact up to 1 year |
| Duration of assigned treatment strategy | During hospitalization (unless otherwise specified in description of arm) |
| Population | Adult patients hospitalized for COVID-19 |
| Study Sites | Approximately 400 sites |
| Number of participants | The sample size is described in each arm-specific appendix. |
| Description of Study Agents | Randomized arms- see appendix This platform trial allows for multiple therapies to be investigated in this trial over time. The trial is governed by a Master Protocol that describes the trial design, endpoint collection, primary endpoint, and inclusion/exclusion criteria. Different therapies, referred to as arms, are detailed in arm-specific appendices. These arm-specific appendices work in a modular fashion as arms are removed and added to the platform trial. |
| Key Procedures | Observation during hospitalization, contact at 90 days post-enrollment, and collection of standard of care laboratory results. Ancillary biobanking will be completed in consenting patients at capable centers. |
1 Introduction, Background Information and Scientific Rationale

1.1 Background Information, Significance and Relevant Literature

The severe acute respiratory syndrome coronavirus 2, which causes the highly contagious coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. The clinical spectrum of COVID-19 infection is broad, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and death. The risk of thrombotic complications is increased, even as compared to other viral respiratory illnesses, such as influenza (1-4). A pro-inflammatory cytokine response as well as induction of procoagulant factors associated with COVID-19 has been proposed to contribute to thrombosis as well as plaque rupture through local inflammation (5). Patients with COVID-19 are at increased risk for arterial and vein thromboembolism (6), with high rates observed despite thromboprophylaxis (7). Autopsy reports have noted micro and macro vascular thrombosis across multiple organ beds consistent with an early hypercoagulable state (8).

Notably, in COVID-19, data in the U.K. and U.S. document that infection and outcomes of infection are worse in African and Hispanic descent persons than in other groups. The reasons for this are uncertain.

Viral Infection and Thrombosis

A large body of literature links inflammation and coagulation; altered hemostasis is a known complication of respiratory viral infections (9-11). Procoagulant markers are severely elevated in viral infections. Specifically, proinflammatory cytokines in viral infections upregulate expression of tissue factor, markers of thrombin generation, platelet activation, and down-regulate natural anticoagulant proteins C and S (11).

Studies have demonstrated significant risk of deep venous thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) associated with viral respiratory infections (10,12). In a series of patients with fatal influenza H1N1, 75% had pulmonary thrombi on autopsy (a rate considerably higher than reported on autopsy studies among the general intensive care unit population (13). Incidence ratio for acute myocardial infarction in the context of Influenza A is over 10 (14). Severe acute respiratory syndrome coronavirus-1 (SARS CoV-1) and influenza have been associated with disseminated intravascular coagulation (DIC), endothelial damage, DVT, PE, and large artery ischemic stroke (11,15). Obi et al. found that patients with Influenza H1N1 and acute respiratory distress syndrome (ARDS) had a 23.3-fold higher risk for pulmonary embolism, and a 17.9-fold increased risk for deep vein thrombosis (16). Compared to those treated with systemic anticoagulation, those without treatment were 33 times more likely to suffer a VTE (16).

Thrombosis, both microvascular and macrovascular, is a prominent feature in multiple organs at autopsy in fatal cases of COVID-19 (8). Thrombosis may thus contribute to respiratory failure, renal failure, and hepatic injury in COVID-19. The number of megakaryocytes in tissues is higher than in other forms of ARDS, and thrombi are platelet-rich based on specific staining. Thrombotic stroke has been reported in young COVID-19 patients with no cardiovascular risk factors (17). Both arterial
and venous thrombotic events have been seen in increasing numbers of hospitalized patients infected with COVID-19. The incidence of thrombosis has ranged from 10 to 30% in hospitalized patients; however, this varies by type of thrombosis captured (arterial or vein) and severity of illness (ICU level care, requiring mechanical ventilation, etc.).

D-dimer, a biomarker of fibrin formation and degradation, is elevated in conditions associated with thrombosis, and has been strongly associated with increased mortality among patients with COVID-19 (1, 2, 3, 6, 7). In a retrospective analysis of 191 patients with COVID-19, Zhou et al. found that non-survivors were more likely to have D-dimer levels > 1 ug/mL than survivors (81% v 24%) (5). Similarly, in a study of 183 patients, Tang et al. noted that non-survivors had significantly higher D-dimer values on admission than survivors (2.12 v 0.61 ug/mL, P < 0.001) (6). In a retrospective study, patients with COVID-19 and D-dimer values > 6-fold upper limit of normal had lower 28-day mortality when treated with prophylactic anticoagulation compared with no anticoagulation (32.8% v 52.4%, p=0.017) (8). Data suggest a strong association between D-dimer and the outcomes of ICU intubation and all-cause mortality, and the association between D-dimer and (1) mortality, (2) critical illness, (3) acute kidney injury, and (4) thrombotic risk is increased at a D-dimer between 1X to 2X the upper limit of normal. Thrombosis is also increased in those with elevated inflammation indexed by C-reactive protein level (20). Preliminary data suggest that platelet activity is increased in COVID-19(18) and that biomarkers of platelet activity correlate with the incidence of death or thrombosis in hospitalized patients with COVID-19. Platelet-fibrin thrombi have been observed in alveolar capillaries, where they may affect gas exchange (8), and in the renal peri-tubular capillaries, where they may contribute to acute tubular necrosis and renal dysfunction. Consistently, autopsy findings demonstrate an increase in the number of circulating megakaryocytes outside the bone marrow and lung. Finally, thrombotic events have been noted – even among patients treated with full dose anticoagulation.

There may be racial and ethnic differences in response to COVID-19 infection. It is hypothesized that antithrombotic interventions being tested will benefit all patients, including those who are disproportionately affected. (21–25, 26).

The ACTIV-4 ACUTE investigators postulate that an antithrombotic regimen will improve clinical outcomes in COVID-19 patients. This protocol intends to define the optimal regimen in an adaptive randomized trial of patients hospitalized with COVID-19 at risk for adverse clinical outcomes. The primary outcome will be the number of days free of organ support within 21 days after randomization. This primary outcome was selected because thrombosis is thought to contribute to the pathogenesis of multi-organ failure in COVID-19, because it is pragmatic and yet clinically relevant, and to align with ongoing studies that may or may not involve antithrombotic therapy, in a time frame relevant to acute illness. Organ support free days is defined by days in which patient is not on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support (see Appendix 2), with death assigned the value of −1 days.

1.1.1 Adaptive Design
This platform trial will have multiple arms, which may be dropped or added as the platform trial progresses. Sample size will be flexible: the trial will be stopped for efficacy or futility based on predetermined statistical thresholds as defined in the arm-specific appendices. Each arm will have an adaptive component for determinations of futility or success.

1.2 Potential Risks & Benefits
See arm-specific Appendices for details
2 Study Design

2.1 Overall Study Design
This trial design is built as a process – with the possibility of multiple interventions being investigated. The trial is designed to be flexible, and these flexible aspects are planned as part of the protocol. This trial may incorporate a flexible number of interventions, and the number of interventions may evolve as the science evolves. Intervention arms will be added or dropped based on criteria defined in arm-specific appendices. Co-enrollment in other trials is permitted as long as the other trial does not test agents with antithrombotic properties and there is no other scientific contraindication.

2.2 Randomization
Randomization assignments are at the participant level and are assigned at baseline. Randomization will be stratified by enrolling site and may also be stratified by severity of illness and/or other arm-specific criteria. In general, allocation will be equally distributed across arms for which the participant is eligible, but may be altered with future arm-specific appendices.

3 Objectives and Purpose
The overarching objective of this adaptive platform design is to iteratively learn which antithrombotic strategy is the best for reducing the primary, secondary, and safety outcomes. Additional alternative strategy(-ies) will be compared to the current standard of care arm, which may trigger new standard of care designated arms as appropriate based on interim analysis results and evolving literature. This process will continue until no new strategies replace the standard of care or potential options for additional antithrombotic interventions are exhausted.
4 Study Design and Endpoints

4.1 Description of Study Design

This trial design is built as a process – with the possibility of multiple interventions being investigated. This is an open label randomized trial of patients hospitalized for COVID-19 who are assigned to different antithrombotic regimens.

4.2 Study Endpoints

4.2.1 Primary Study Endpoint

21 Day Organ-Support free-days. The primary endpoint is the number of days that a patient is alive and free of organ support through 21 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of −1.

4.2.2 Secondary Endpoints

- **Key Secondary Endpoint:** A composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization or at 28 days after enrollment (whichever is earlier)

**Other Secondary Endpoints:**
- A composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization or at 28 days after enrollment (whichever is earlier)
- 28 Day Hospital free days (non-ICU level patients)
- 28 Day Ventilator-Free Days (ICU level patients)
- 28 Day Vasopressor-Free Days (ICU level patients)
- 28 Day Renal Replacement Free Days
- Hospital readmission within 28 days
- Acute kidney injury as defined by KDIGO criteria
- Deep vein thrombosis
- Pulmonary embolism
- Systemic arterial thrombosis or embolism
- Myocardial infarction
- Ischemic stroke
- Use of extracorporeal membrane oxygenation (ECMO) support
- Mechanical circuit (dialysis or ECMO) thrombosis
- All-cause mortality at 28 days
- Organ support free days at 28 days
- All-cause mortality during initial hospitalization (includes death after 28 days)
- WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)
- All-cause mortality at 90 days
4.2.3 Additional Study Endpoints
- Individual endpoints of the thrombotic endpoint
- Length of Hospital stay
- Exploratory endpoints (subset of sites)
  - Cardiac injury (e.g., troponin)
  - Trajectories of biomarkers related to COVID-19
  - DIC
See arm-specific Appendices for additional tertiary endpoints of interest specific to arm.

4.2.4 Safety Endpoints
- Major Bleeding (as defined by the ISTH)
- Symptomatic intracranial or intracerebral hemorrhage (evaluated as a separate endpoint from other major bleeding) (19)
- Confirmed Heparin induced thrombocytopenia (laboratory confirmed by anti-PF4 test or Serotonin Release Assay (SRA))

5 Study Enrollment

5.1 Inclusion Criteria
In order to be eligible to participate in this study, an individual must meet all of the following criteria:
- \( \geq 18 \) years of age
- Hospitalized for COVID-19*
- Enrolled within 72 hours of hospital admittance or 72 hours of positive COVID test
- Expected to require hospitalization for > 72 hours
- See arm-specific Appendices for additional criteria and details

*It is strongly recommended to confirm SARS-CoV2 with a positive PCR or other commercial or public health assay prior to randomization. At centers where there is a delay in confirming the diagnosis, a sufficiently high clinical suspicion is sufficient to proceed with randomization as long as confirmation is expected within 24 hours.

5.2 Exclusion Criteria
- Imminent death
- Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization
- Pregnancy
- See arm-specific appendices for additional criteria and details.

5.3 Vulnerable Subjects
Critically ill patients with COVID-19 may not have capacity to provide consent. This trial will include participants who have no capacity to consent only if their legal proxy is able to consent on their behalf. It has become increasingly apparent that individuals with COVID-19 are at risk for thrombotic (and bleeding) events. Patients without the capacity to consent for themselves will have a potential for direct benefit by being part of the trial.

Participation in this trial is expected to facilitate careful monitoring of both thrombotic and bleeding endpoints, which may benefit participants.
Capacity assessment will be conducted by the treating physician or an independent medical provider with appropriate expertise based on the standard clinical assessment of capacity and communicated to the study team. Surrogate consent will be provided by the subject’s Legally Authorized Representative as defined by local policies and state/country regulations.

Consent will be obtained from the LAR before any study related procedures begin. Participants’ capacity will be monitored throughout the study by working with the treatment team. Once the participant regains the capacity to consent, they will be informed of their participation in the study and will have an opportunity to withdraw from further participation in the study. The enrollment of patients without capacity is important because critically ill patients, especially those who are not ambulatory, are at higher risk of developing clotting complications.

5.4 Strategies for Recruitment and Retention
Listings of patients admitted to the participating sites with COVID-19 may be reviewed for eligibility by the study team, to identify and recruit potential participants, until study enrollment goals have been met. The study team should communicate with the inpatient care team. All treating physicians will be informed of the study and will have the option to advise of any conditions that would preclude any individual patient being approached.

5.5 Duration of Study Participation
Duration of study participation is, 90 days from enrollment. Participants may be contacted for follow-up for approximately one year.

Total Number of Participants
The total sample size for the Platform trial is not pre-determined. The sample size for each arm will be set in the arm-specific appendix and will incorporate an adaptive design. There will be interim monitoring to allow early stopping for futility, efficacy, or safety. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs. Some arms may not relate solely to antithrombotic therapy.

5.6 Participant Withdrawal or Termination
5.6.1 Reasons for Withdrawal or Termination
Participants are free to withdraw from participation in the study at any time upon request. Discontinuation of a study agent, regardless of the reason, e.g. patient or physician request, or adverse event, does not constitute study withdrawal. Patient data will still be collected as planned and analyzed as intent to treat unless the participant withdraws consent for continued follow-up. An investigator may terminate participation in the study if:

- Any situation occurs such that continued participation in the study would not be in the best interest of the participant

5.7 Premature Termination or Suspension of Study
All deaths and DSMB-specified severe adverse events within the study period will be reviewed by the DSMB. The decision to stop or suspend the study, or an arm of the study, will be made by the DSMB after considering the totality of the data and the benefit-risk of continuing the study.

This study, or an arm of the study, may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in a strategy, such as excess mortality and/or major bleeding (this will be determined by the oversight data safety monitoring plan)
- Demonstration of efficacy or lack thereof that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent and Procedural Intervention

6.1 Study Agents
Each arm in this platform trial will include different treatment strategies. Information about the treatment strategies for a given arm can be found in the arm-specific appendices.

6.2 Duration of Therapy
Once participants are randomized to a treatment strategy (arm), they will remain on treatment for the duration specified by the relevant appendix. However, if a participant randomized to one arm develops an indication for a different strategy (e.g., thrombotic event, worsening clinical status), the participant will be treated based on institutional guidelines with any measures required by local clinical judgment.

7 Study Procedures and Schedule

7.1 Study Schedule

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening/Enrollment</th>
<th>Hospital Duration</th>
<th>28 days and/or hospital discharge***</th>
<th>90-days post randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Demographic and Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Assessment of Inclusion/Exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported race/ethnicity and gender</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug Administration</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Procedures
Height
Weight
Vital signs
Concomitant medications
WHO ordinal assessment
Outcomes Assessment
SOC Laboratory Assessments
Chemistry panel
Hematology panel
D-dimer*
Blood Group**

See arm-specific appendices for additional measures

*D-dimer is strongly recommended for measurement in all participants as close to the time of randomization as feasible.
**Blood group will come from hospital record or self report if available. Biospecimens see appendix 4.
***Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge)

Laboratory Procedures/Evaluations
See arm specific appendices.

All analyses will be performed on SOC labs and procedures done for usual care. The standard operating procedures for samples to be collected for research purposes are included as Appendix 5. All research samples will be timed with clinical lab draws to limit provider exposure. Collection of research samples as outlined in Appendix 5 is strongly encouraged where safe and feasible.

7.1.1 Visit 1 and Hospitalization Visits (see arm-specific appendices for details)

Visit 1 (Screening and Randomization)
1. Informed consent obtained
2. Assessment of inclusion/exclusion criteria assessed
3. Screening, consisting of reviewing participant medical history and information in their chart such as height, weight, vital signs, and normal clinically performed laboratory assessments, including pregnancy test for all women of childbearing age.
4. If confirmed eligible, following randomization, initiation of treatment with the assigned strategy

Hospitalization Visits
1. Recording of specifics of study treatment according to assigned arm
2. Laboratory assessments as part of standard of care
3. Daily WHO ordinal assessment
4. Ongoing daily outcomes and safety assessment
7.1.2 28 days and/or Date of Hospital Discharge
   1. Recording of outcomes and safety assessments as reported by participant or observed by investigator
   2. WHO Ordinal Assessment
   3. Recording of vital status and ascertainment of events
   4. Recording of participant’s adherence to treatment strategy, if patient is in hospital

These assessments will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days.

Participants may be contacted by a research contact and/or by the participating hospital study team periodically for longer term follow-up for approximately a year. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge). Discharge visits must be completed.

7.2 Concomitant Medications, Treatments, and Procedures
Concomitant medications taken during study participation will be recorded on the case report forms (CRFs). Concomitant medications to be recorded are:
- Other antithrombotics (e.g., aspirin and other antiplatelet agents)
- Any medications used for the treatment of COVID-19 infection (e.g., remdesivir, steroids, IL-6 inhibitor such as tocilizumab)
- Others specified in arm-specific appendices

7.3 Expedited Critical and Major Event Reporting
All efficacy and safety outcome events will be assessed and documented in the participants’ study records. The ACTIV-4 Platform will have a uniform policy for reporting adverse events to ensure that all events are assessed quickly and are submitted to the DSMB, IRB(s), and other groups as needed (e.g., FDA), following each group’s reporting guidelines and timelines. Events meeting the independent DSMB-specified criteria will be reported immediately and within the time frames specified by the DSMB.

Sites are required to follow their local reporting guidelines.

7.4 Data and Safety Monitoring Plan and Study Halting Rules
The ACTIV-4 Platform will have a uniform Data and Safety Monitoring Plan, encompassing all research carried out within the Platform.

8 Statistical Considerations

8.1 Statistical and Analytical Plans (SAP)
There will be a formal Statistical Analysis Plan (SAP) and each arm added to the trial will have its own arm-specific SAP. This will include the primary analysis, the primary comparison, futility and success rules, and interim analysis schedule. The SAP will be created prior to the first interim analysis for the study and each arm-specific SAP will be created before the first interim analysis for that arm.
8.2 Statistical Modeling for the Primary Analysis

Inferences in this trial are based on a Bayesian statistical model for the ordinal primary outcome, organ-support free-days (OSFD). There is a single Bayesian model for the primary outcome across each arm and subpopulation. The Bayesian model is an ordinal cumulative logistic regression model described below.

Let \( Y_i \) denote the ordinal outcome (OSFD) for patient \( i \). The probability of patient \( i \) observing \( y \) OSFD or less is denoted as \( \pi_{iy} = \Pr(Y_i \leq y) \). The parameters in the model are structured so that a value > 0 implies treatment benefit, and hence an odds-ratio > 1 implies treatment benefit. In this section we describe the generic model for the study, but arm-specific appendices may vary in its modeling assumptions. The generic primary analysis model is formulated as follows:

\[
\log\left( \frac{\pi_{iy'}}{1 - \pi_{iy'}} \right) = \alpha_{y,s} - [\psi_{Site,s} + \lambda_{Time,s} + \theta_{a,s,d} + \beta_{Age,s} + \beta_{Sex,s} + \beta_d]
\]

1. The “subtype” variable, \( s \), corresponds to the two patient subgroups defined by disease severity:
   a. subtype = 1 is non-ICU level care
   b. subtype = 2 is ICU-level care

2. The d-dimer level for a patient, \( d \), is classified for a patient as
   a. \( d=1 \) is a low or unknown d-dimer level
   b. \( d=2 \) is a high d-dimer

   The d-dimer level is only used for non-ICU (\( s=1 \)) patients. We use the notation \( s:d \) to imply the parameterization would be \( s=1, d=1 \) (non-ICU level care, low d-dimer); \( s=1, d=2 \) (non-ICU level care, high d-dimer); and \( s=2 \) (ICU care).

3. The “site” variable is the clinical site within the trial. These will be site effects estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.

4. The “time” variable is an indicator of the month of enrollment in the trial, numbered decreasing from the first enrollment to the last enrollment for the analysis. The time effects will be estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.

5. The “arm” the patient is randomized to is labeled as \( a \). The effects of arm are modeled by both the disease state and the d-dimer level.

6. The “age” variable is a categorical classification of age as \( \leq 39 \), 40-49, 50-59, 60-69, 70-79, and 80+. The age effects will be estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.

7. The “sex” variable is sex at birth. The sex effects will be estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.

If additional covariates (e.g. race and ethnicity) are added to the model they will by default, unless otherwise specified, vary by disease state, but not d-dimer levels.
The $\alpha_{y,\text{subtype}}$ parameters are the baseline rates of the ordinal outcome, which are modeled separately by disease subtype. The additive effects of d-dimer levels are modeled with the $\beta_d$.

### 8.3 Model Priors

The treatment effects for arm $a$, within disease subtype $s$ and d-dimer level $d$ are modeled with the $\theta_{a,s,d}$ parameters. The $\beta$ parameters model any covariate effects included in the model. The $\lambda$ parameters model the effect of time within the pandemic.

The ordinal endpoint rates are modeled using an inverse Dirichlet model where the individual probabilities for the 24 outcomes are based on 1 patient's weight on real-world evidence-based outcomes. The weight for each of the outcomes will be assumed equal.

\[
\logit(\alpha_{y,s}) \sim \text{Dirichlet}(1 \ast P), \text{where } P \propto 1
\]

The site effects, $v_{\text{Site}}$, are modeled using a hierarchical model where site is nested within the country of the site:

\[
v_{\text{Site},s} \sim N(\mu_{\text{country},s}, \tau_{\text{country},s}^2) , s = 2, \ldots, N_{\text{Site}}
\]

\[
\mu_{\text{country},s} \sim N(0,1); \quad \tau_{\text{country},s}^2 \sim IG(0.25,0.1), s = 1,2
\]

A referent site, expected to be the largest enrolling site, will be set such that $v_{\text{Site}} \equiv 0$. The hyper-parameters of the site hierarchical model are separate by disease state $s$.

The effect of time ($T$) is modeled using a second-order normal dynamic linear model separately by disease state, $s$. The most recent two time periods are modeled as the referent time epochs with the time parameters set to 0. The preceding time epochs are modeled as a normal dynamic linear model as:

\[
\lambda_1 = \lambda_2 \equiv 0
\]

\[
\lambda_3 \sim N(0,0.15^2)
\]

\[
\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0,\tau_{\text{time}}^2) , T \geq 4
\]
The treatment effect parameters are set against a control arm, which will be labeled in the arm-specific appendix. The treatment effect for the control arm, labeled as arm $a = 1$, will be set to 0 for each of the disease subtype and d-dimer level:

$$\theta_{1,\text{subtype},d} = 0$$

The effect of each treatment arm introduced will typically be modeled hierarchically across disease subtypes and/or d-dimer levels. The modeling of the treatment arms will be specified in appendices.

Any additional covariates included in the model will have independent $N(0,1)$ priors unless otherwise specified.

### 8.4 Assessing Effectiveness

The treatment effect parameters, $\theta$, represent the log-odds ratio, of the treatment, for the cumulative logistic for the ordinal model. In this parametrization an odds ratio $> 1$, or a log-odds ratio $> 0$, signifies improved outcomes relative to the referent control treatment. The odds-ratio parameter $\exp(\theta)$, labeled OR, will be used to summarize the treatment effect relative to control or $\exp(\theta_{a_1} - \theta_{a_2})$ for the odds-ratio between arms $a_1$ and $a_2$. The posterior mean, median, standard deviation, and 95% credible intervals for the odds-ratio will be used to summarize relative treatment effects.

The posterior probability that an arm, $a_1$, is superior to another arm, say, $a_2$, is:

$$\Pr(\theta_{a_1} > \theta_{a_2}).$$

This probability will be used for triggers of superiority of one arm to another arm.

The posterior probability that an arm, $a_1$, is superior to another arm, say, $a_2$, by a specified difference on the odds-ratio scale is:

$$\Pr(\exp(\theta_{a_1}) > \exp(\theta_{a_2}) + \delta).$$

This probability will typically be used for futility. If the probability is small that a treatment has benefit above a control of some specified amount ($\delta$), the arm may be dropped for futility.

### 8.5 Analysis Datasets

The intention-to-treat (ITT) analysis dataset will be the source of data for primary analyses. This will include all randomized participants regardless of actual receipt or compliance with therapy. The safety analysis set will consist of all participants who received at least one dose of study
medication. The per protocol analysis will be conducted based on adherence to assigned treatment; this dataset will support sensitivity analyses to complement the primary ITT analyses.

The ITT group for an arm consists of the participants that were randomized in the platform that were eligible to be randomized to that arm. This may vary from the platform ITT population, which consists of all participants randomized.

Participants who are randomized to receive one strategy may in fact be treated with another strategy based on health status and provider discretion. Exploratory analyses will estimate the causal effect of the treatment for these participants using marginal structural modelling techniques. These techniques use inverse probability weighting methods that are based on patient-level covariates to create comparable groups for the analysis.

8.5.1 Safety Analyses
Monitoring for safety will be conducted continuously. For each arm-specific appendix potential adverse events of importance will be identified. A Bayesian monitoring rule will be used to summarize the adverse event rates across all arms for the adverse events of importance within each arm-specific appendix. A Bayesian prior distribution of a beta (0.1, 0.9) will be used to model the likelihood of each adverse event of importance. For each adverse event of importance, the posterior mean event rates, the posterior mean of the difference between each arm, and the 95% credible intervals for the risk-difference and odds-ratio will be summarized.

8.5.2 Adherence and Retention Analyses
The primary analysis is by intention to treat. Per protocol analysis will be conducted based on adherence to assigned treatment. For any scheduled follow-up post hospital discharge every effort will be made to recontact participants who are unreachable. Due to the short trial participation timeline, excellent patient retention is anticipated.

8.5.3 Baseline Descriptive Statistics
All variables will be summarized using mean, median, standard deviation, and range (for continuous variables) and frequency (for categorical variables). Treatment groups will be compared with respect to baseline characteristics to verify randomization balance.

8.5.4 Planned Interim Analysis
An independent data safety and monitoring board (DSMB) will review all interim analyses prepared by an unblinded statistical analysis committee.

8.5.5 Safety Review
Monitoring for safety will be conducted continuously. The DSMB will be monitoring safety for each arm-specific appendix. The DSMB monitoring plan includes guidance on stopping specific arms for safety concerns.

8.5.6 Tabulation of Individual Response Data
The composite outcome evaluated will be tabulated and broken down by component (e.g., death, pulmonary embolus, symptomatic DVT, myocardial infarction, etc.). Note that some participants may experience more than one component of the primary endpoint.
8.5.7 Exploratory Analyses
Exploratory analyses will be conducted in a subset of participants on whom additional clinical and basic science assays are performed. These will be descriptive and hypothesis-generating.

8.6 Sample Size
Sample size for the platform trial is not pre-determined. The platform trial will run as long as there is a need and there are investigational arms enrolling. The sample size for each arm will be specified in the arm-specific appendix. Interim analyses for each arm will take place in the platform trial and detailed in the arm-specific appendix. Conclusions of futility or superiority may be drawn specific to a patient subtype. Effort will be taken to conduct all interim analyses at the same time in the platform trial since there is a single Bayesian model of the efficacy of all arms conducted. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs.

Generic sample size calculations for an ordinal endpoint of 21-day OSFD with a maximum sample size of 1000 for an investigational arm, compared to a second control arm with 1000 participants (2000 participants total), yields over 80% power for an odds-ratio change of 1.25 on the OSFD endpoint. An odds ratio of 1.5 has approximately 90% power for 400 participants per arm. An odds-ratio of 2 results in more than 90% power for the first interim analysis of 200 participants per arm. An updated sample size estimate for additional arms is provided in Appendix 1.3.

9 Measures to Minimize Bias

9.1 Enrollment/Randomization

Enrollment

1. Patients hospitalized for COVID-19 are screened daily within the eligibility time window for inclusion/exclusion criteria. Any patient who meets all inclusion criteria and no exclusion criteria will be approached for enrollment.

2. Patients remain in the intention-to-treat group if they meet the criterion for another treatment strategy after randomization.

10 Randomization
Randomization assignments are performed for participants at baseline. Randomization will be equal across all arms a patient is eligible. Randomization stratification will be done by site, and disease subtype (ICU and non-ICU level care) and/or other arm-specific criteria.

11 Source Documents and Access to Source Data/Documents
The ACTIV-4 Platform will have uniform policies describing what source documents are, how to make corrections, and who can access them.
12 Quality Assurance and Quality Control
The ACTIV-4 Platform will have uniform policies for quality assurance at the data entry level and site monitoring.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard
The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants
Consent forms describing in detail the study agent, study procedures, and risks are given to the participant, and written documentation of informed consent is required prior to starting intervention/administering study product.

A written consent will be sought from every participant via a face to face consenting process or remotely by using an e-consent option as per IRB approved method.

13.3.2 Consent Procedures and Documentation
Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained following institutional COVID policy to protect study staff.

An extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be provided to participants. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
Participants who have no capacity to consent for themselves will have a surrogate consenting process via legally authorized representative.

13.4 Posting of Clinical Trial Consent Form
The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

13.5 Participant and Data Confidentiality
The ACTIV-4 Platform will have uniform policies for protecting the privacy of participants and maintaining confidentiality. These policies will adhere to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities
The ACTIV-4 Platform will have uniform policies for data management.

14.2 Study Records Retention
The ACTIV-4 Platform will have uniform policies for records retention.

14.3 Protocol Deviations
A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy
The ACTIV-4 Platform will have uniform policies for publications and data sharing.

15 Study Finances

15.1 Funding Source
National Institutes of Health
15.2 Costs to the Participant
Participant health insurance may be billed for the costs of medical care during this study since these expenses would have happened even if the participant were not in the study. If the participant’s insurance does not cover these costs or the participant does not have insurance, these costs will be participant’s responsibility.

16 Conflict of Interest Policy
The ACTIV-4 Platform will have uniform policies for identifying and disclosing potential conflicts of interest.

17 References
Appendix 1: Master Protocol State of Arms

This appendix will be updated as arms are added or dropped. The current version and version history appear below.

Version 21AUG2020 1AB: Outlined possible example scenarios for adaptive design. Arms A and B included.
Version 01FEB 2021: Adds Arms C and D (Appendices 7 and 8), implements suspension of Arm A in participants with ICU level of care (severe illness) at the time of randomization due to futility, and suspension of Arm B for non ICU level of care participants (moderate illness) at the time of randomization, due to superiority of Arm A.

See Appendix 1.1 for current state of arms in severely ill participants and 1.2 for current state of arms in moderately ill participants.

Randomization: Randomization assignments are at the participant level, stratified by enrolling site and by ICU level of care vs non-ICU level of care and/or other arm-specific criteria.
Appendix 1.1 ICU LEVEL OF CARE (SEVERE) COHORT

Overview of Addition of P2Y12 Antiplatelet Agent Arm C to existing Arm B for ICU Level of Care (Severe) Cohort

There are currently two arms in the master protocol for patients in the severe/ICU-level of care cohort.

For the ICU level of care cohort (severe), the treatment arms and arm-specific appendices are:

- Arm B: Prophylactic-dose anticoagulation, no P2Y12 inhibitor, Appendix 4
- Arm C: Prophylactic-dose anticoagulation, plus P2Y12 inhibitor, Appendix 7

Each participant is randomized equally among each of the arms for which they are eligible.

*Participants who ARE receiving ICU level of care at the time of randomization will be randomized to Arm B or Arm C.*

<table>
<thead>
<tr>
<th>Anti-thrombotic Drug</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>Prophylactic-dose</td>
<td>Prophylactic-dose</td>
</tr>
<tr>
<td>Antiplatelet: P2Y12 inhibitor</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Appendix 1.2. NON-ICU LEVEL OF CARE (MODERATE) COHORT

Overview of Addition of P2Y12 Antiplatelet Agent Arm D to existing Arm A for non-ICU Level of Care (Moderate) Cohort

There are currently two arms in the master protocol for the non-ICU-level of care/moderate cohort.

For the non-ICU level of care (moderate) cohort, the treatment arms and arm-specific appendices are:

Arm A: Therapeutic-dose anticoagulation, no P2Y12 inhibitor, Appendix 3
Arm D: Therapeutic-dose anticoagulation, plus P2Y12 inhibitor, Appendix 8

Each participant is randomized equally among each of the arms for which they are eligible.

Participants in the non-ICU level of care cohort at the time of randomization will be randomized to Arm A or D (See Appendix 8 for eligibility criteria):

<table>
<thead>
<tr>
<th>Anti-thrombotic Drug</th>
<th>Arm A</th>
<th>Arm D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>Therapeutic-dose</td>
<td>Therapeutic-dose</td>
</tr>
<tr>
<td>Antiplatelet: P2Y12 inhibitor</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Appendix 1.3. Current Statistical Modeling and Adaptions

This section presents the current statistical modeling assumptions for the current status of the master protocol (as of 01 FEB 2021).

In the master protocol there will be two subtypes where arms will be compared. Arm C will be compared to Arm B in the ICU (severe) subtype (cohort) and Arm D will be compared to Arm A in the non-ICU (moderate) subtype (cohort). In the moderate subtype there will not be analyses by D-dimer levels in the primary analysis.

Adaptations and Conclusions:
Interim analyses are expected to be carried out periodically in this platform with frequency potentially varying by enrollment. The expectation is that interim analyses would occur approximately every 200 patients enrolled to each subtype, no more frequently than monthly.

At each interim analysis the following conclusions could be triggered:

1. In the Moderate State, Arm D can be found superior to Arm A on the primary endpoint. If the posterior probability that Arm D is superior to Arm A on the primary endpoint is at least 99% then the conclusion of superiority of Arm D to Arm A will be made.
2. In the Moderate State, Arm D can be found futile compared to Arm A on the primary endpoint. If the posterior probability that Arm D has at least a 1.2 odds-ratio improvement on the primary endpoint compared to Arm A is less than 5% then the conclusion of futility of Arm D to Arm A will be made.
3. In the Moderate State, Arm D can be found inferior to Arm A on the primary endpoint. If the posterior probability that Arm D is superior to Arm A on the primary endpoint is less than 1% then the conclusion of inferiority of Arm D to Arm A will be made.
4. In the Severe State, Arm C can be found superior to Arm B on the primary endpoint. If the posterior probability that Arm C is superior to Arm B on the primary endpoint is at least 99% then the conclusion of superiority of Arm C to Arm B will be made.
5. In the Severe State, Arm C can be found futile compared to Arm B on the primary endpoint. If the posterior probability that Arm C has at least a 1.2 odds-ratio improvement on the primary endpoint compared to Arm B is less than 5% then the conclusion of futility of Arm C to Arm B will be made.
6. In the Severe State, Arm C can be found inferior to Arm B on the primary endpoint. If the posterior probability that Arm C is superior to Arm B on the primary endpoint is less than 1% then the conclusion of inferiority of Arm C to Arm B will be made.

The primary statistical model in the Master protocol will be used with the following alterations. There will be no modeling of the d-dimer subtypes in the moderate state. In the statistical model there are two parameters of treatment effects, the effect of adding P2Y12 to therapeutic dose anticoagulation (effect of Arm D compared to Arm A) in the moderate state, \( \theta_{D,1} \). In the severe state the effect of adding P2Y12 to the prophylactic-dose anticoagulation (effect of Arm C to Arm B) is \( \theta_{C,2} \).

The two efficacy parameters, \( \theta_{D,1} \) and \( \theta_{C,2} \) are modeled hierarchically:

\[ \theta_{D,1}, \theta_{C,2} \sim N(\mu_{CD}, \tau_{CD}^2) \]

With hyperpriors
The start of Arms C and D will trigger the inferential comparison between Arm C to Arm B and Arm D to Arm A, thus the analysis for these comparisons will start when the randomization begins for these arms. No data from before the randomization of arms C and D will be used in the primary analysis for these comparisons. Sensitivity analyses will be conducted comparing patients on Arms A and B before and after the inclusion of arms C and D.

Sample Size Expectations

The relevant comparison with Arms A, B, C and D in the Master protocol is the effect of adding P2Y12 separately in moderate and severe patients in whom there is a different standard of care heparin dose. The sample size calculations present the power for the effect of adding the P2Y12 for an ordinal endpoint of 21-day OSFD with a maximum sample size of 1000 for an investigational arm (adding P2Y12), compared to a control arm with 1000 participants (2000 participants total). This yields over 80% power for an odds-ratio change of 1.25 on the OSFD endpoint. There will be approximately 90% power for an odds ratio of 1.5 with 400 participants per arm. An odds-ratio of 2 results in more than 90% power for the first interim analysis of 200 participants per arm.

Based on these estimates, we expect that 500 patients per arm will be sufficient to reach a conclusion. Thus the sample size is expected to be a maximum of 1000 patients enrolled to Arms C and D with 1000 enrolled to Arms A and B, for 2000 patients total across the 4 arms. If the enrollment is differential across the arms there may be a need for a larger total sample size.
Appendix 2: Definition and Determination of Outcomes

A2.1 Approach to ascertainment and verification of outcomes
Outcomes are assessed locally and will not be centrally adjudicated in this pragmatic trial platform, except as specified in the arm-specific appendix. Outcomes should be assessed by a local investigator or other qualified study team member who is blinded to treatment assignment, using the definitions below.

A2.2 Outcome definitions

21 Day Organ-Support Free-Days (OSFD)
Defined as the number of days that a patient is alive and free of organ support through 21 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of –1.

- Non-invasive mechanical ventilation is defined as BIPAP or CPAP when used for acute respiratory support (the use of BIPAP or CPAP at night or when sleeping for sleep apnea is not considered organ support).
- High Flow Nasal Cannula Oxygen is defined as delivery of oxygen through a system that typically delivers oxygen at 20 to 60 liters per with a titratable FiO2.
- Invasive mechanical ventilation is defined as positive pressure ventilation through endotracheal tube or tracheostomy.
- Vasopressor support includes infusion of any vasopressor or inotropic medication.
- Any patient dying in the acute hospital stay (even if beyond day 21) are assigned 21 Day Organ-Support Free Days of –1.
- If there is intervening time in which a patient is free of organ support but goes back on organ support the intervening time does not count toward the organ support free days endpoint. Only time before organ support and after the last use of organ support are counted as “free days.”
- If a patient was discharged alive without mechanical ventilation prior to Day 21, the patient is assumed to be free of organ support after hospital discharge for the remainder of the 21 days.
- If a patient was discharged alive on mechanical ventilation prior to Day 21, a call to the discharge facility is needed to confirm ventilation status on Day 21 and the last day on mechanical ventilation.

Primary Endpoint

Days free of organ support within 21 days after randomization. Organ support free days (OSFD) is defined as days in which patient is not on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, or vasopressor therapy or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of –1.
To be specific about which organ support was affected, secondary outcomes include: ventilator free days, renal replacement free days, vasopressor free days.

Justification for use of OSFD:
- Pragmatic
- Can be calculated from WHO ordinal scores
- Incorporates clinically important need for organ support but also duration of organ support
- No additional data collection is necessary to calculate secondary outcomes of ventilator free days, renal replacement free days, and vasopressor free days to understand which organ support was most impacted
- Incorporates mortality as the worst possible outcome

Secondary Endpoints

Deep vein thrombosis
Deep vein thrombosis will be diagnosed by venous ultrasound or point-of-care ultrasound (POCUS) or other imaging modality and documented in a note, and performed for clinical indications. A positive ultrasound test is defined by a noncompressible or partially noncompressible venous segment and should be reported. Thrombosis may involve the cerebral venous sinus or any venous bed, including the upper extremities. Routine screening for deep vein thrombosis is not recommended. If deep vein thrombosis is diagnosed and treated without imaging due to imaging availability concerns or risk of exposure to SARS CoV-2, this will be classified as probable deep vein thrombosis. Later imaging is preferable in these cases when possible.

Pulmonary embolism
Pulmonary embolism will be confirmed by chest CT with PE protocol, pulmonary angiography or ventilation-perfusion scan. Events may also be defined without this imaging by the care team, as evidenced by, for example, “clot in transit” on echocardiogram. If PE is diagnosed and treated without imaging due to imaging availability concerns or risk of exposure to SARS CoV-2, this will be classified as probable PE. Later imaging is preferable in these cases when possible.

Stroke/ Peripheral Arterial Systemic Thromboembolism
Stroke or systemic embolism as diagnosed by imaging (i.e., head CT, lower extremity CT angiogram) or deemed “highly-likely” by the provider based on physical examination (i.e., acute hemiplegia thought to be due to stroke, acute distal lower extremity hypoperfusion). Systemic thromboembolism may involve the retinal artery, spinal cord or other vascular beds. Classification of ischemic vs. other etiologies is based on neuroimaging. Venous sinus thrombosis will be included in the category of vascular occlusion/ischemic stroke on the venous side. Primary CNS hemorrhage: intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, and rarely epidural hematoma or spinal hematoma. Secondary hemorrhagic stroke: blood associated with an ischemic infarct.

ICU Level of care disease state (severe illness)
Defined as receipt of organ support as defined in the 21-day organ support free days. ICU level of care is defined as being on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, or vasopressor therapy or ECMO support.

Myocardial infarction
Myocardial infarction is defined according to the universal definition of MI, which excludes myocardial injury e.g., isolated elevation of cardiac troponin. MI must include rise and fall of cardiac
troponin above the 99th percentile with at least one of the following: symptoms of acute ischemia, ECG changes consistent with ischemia, new/presumed new wall-motion abnormalities or other imaging evidence of MI, abnormal coronary angiography (e.g. identification of a coronary thrombus).

Acute Kidney Injury
Acute kidney injury after enrollment is defined by KDIGO criteria for Acute Kidney Injury in the setting of not meeting these criteria upon enrollment:

THREE STAGES:
- Stage 1: Serum Cr 1.5–1.9 times baseline, OR ≥ 0.3 mg/dl increase in serum Cr
- Stage 2: Serum Cr 2.0–2.9 times baseline
- Stage 3: Serum Cr ≥ 3.0 times baseline, OR Increase in serum creatinine to ≥ 4.0mg/dl, OR Initiation of renal replacement therapy

Disseminated Intravascular Coagulation (DIC) (Overt) – DIC score ≥ 5
1. Platelet count ≥ 100 K (0); 50–100K (1 point); < 50K (2 points)
2. Elevated D-dimer: no increase (0 points); moderate increase (1 point); severe increase (3 points) according to local criteria.
3. Prolonged PT < 3 seconds (0 points); 3–6 seconds (1 point); ≥ 6 seconds (2 points)
4. Fibrinogen level ≥ 100 (0 points); < 100 (1 point) mg/dL

ISTH Defined Major Bleeding
Bleeding that:
1. Resulted in death,
2. Occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or
3. Associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells or whole blood.

Symptomatic Intracranial or Intracerebral Hemorrhage (sICH)
sICH is defined as any acute extravasation of blood into the brain parenchyma, subarachnoid space, subdural space, or epidural space as demonstrated by imaging or autopsy, associated with any clinical deterioration or death


<table>
<thead>
<tr>
<th>Patient State</th>
<th>Score</th>
<th>Descriptor</th>
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</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>0</td>
<td>No clinical or virological evidence of infection</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>1</td>
<td>No limitation of activities</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Symptomatic: Limitation of activities</td>
</tr>
<tr>
<td>Hospitalized: Mild</td>
<td>3</td>
<td>Hospitalized; no oxygen therapy</td>
</tr>
<tr>
<td>Hospitalized: Severe</td>
<td>4</td>
<td>Hospitalized; oxygen by mask or nasal prongs</td>
</tr>
<tr>
<td>Hospitalized: Severe</td>
<td>5</td>
<td>Non-invasive ventilation or high-flow oxygen</td>
</tr>
<tr>
<td>Disease</td>
<td>6</td>
<td>Intubation &amp; Mechanical ventilation</td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>Ventilation and additional organ support – pressors, RRT, ECMO</td>
</tr>
<tr>
<td>Death</td>
<td>8</td>
<td>Death</td>
</tr>
</tbody>
</table>
Appendix 3: Therapeutic-dose Anticoagulation (Arm A)

Based on DSMB review and NHLBI Determination, as of Dec 19, 2020 patients who require ICU level of care (severe illness) at screening/potential enrollment are NOT eligible for Arm A.

Any of the following strategies are recommended for therapeutic-dose anticoagulation:

### A3.1 Therapeutic Dose Anticoagulation**

<table>
<thead>
<tr>
<th>CrCl</th>
<th>BMI</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30</td>
<td>&lt;40</td>
<td>1 mg/kg SC q12h OR 1.5 mg/kg SC q24h</td>
<td>200 units/kg SC q24h OR 100 units/kg SC q12h</td>
<td>175 units/kg SC q24h</td>
<td>IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*</td>
</tr>
<tr>
<td>≥40</td>
<td></td>
<td>1 mg/kg SC q12h</td>
<td>100 units/kg SC q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>&lt;40</td>
<td></td>
<td></td>
<td></td>
<td>Heparin IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*</td>
</tr>
<tr>
<td>≥40</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* Initial bolus dose determined by sites, encouraging use of dosing algorithm designed for treatment of VTE. UFH anti-Xa titration is preferred over aPTT if available because achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19.

Note: Tinzaparin commonly used in Canada
Note: Fondaparinux not advised in this setting due to its long half life

**These drugs are considered standard of care as an anticoagulant¹. Different drugs are used in different regions, countries, and hospital formularies. In this pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

It is recommended that participants be given therapeutic-dose parenteral anticoagulation daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician. At the time of treatment discontinuation, standard of care antithrombotic prophylaxis should be administered.

If aspirin is to be prescribed, the maximum dose permitted is 162 mg per day. If a P2Y12 was prescribed before randomization, it is stopped at the time of randomization. Note that requirement for P2Y12 inhibitor or for a dose of aspirin greater than 162 mg per day is an exclusion criterion. However, a P2Y12 inhibitor may be used if a clinical indication develops eg, coronary artery stenting. This is not a protocol deviation.

If there is a change in status such that the participant becomes severely ill, continue assigned treatment unless:
  a) There are contraindications
  b) Clinical judgment leads to a change in dose

Follow up continues through 90 days regardless of the change in status.
A3.2 Discontinuation of study intervention:
Patients randomized based on suspicion of COVID-19 whose tests do not confirm SARS CoV2 infection should not continue to receive study assigned therapeutic dose anticoagulation.

Anticoagulation should be discontinued if there is clinical bleeding or other complications sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. The use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, but not longer than 24 hours – such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

A3.3 Study Schedule

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening/Enrollment</th>
<th>Hospital Duration</th>
<th>28 days and/or hospital discharge*</th>
<th>90 days post randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Demographic and Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of Inclusion/Exclusion criteria</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported race/ethnicity and sex</td>
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</tr>
<tr>
<td>Pregnancy Test, for women of childbearing potential</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug Administration</td>
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</tr>
<tr>
<td>Randomization</td>
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</tr>
<tr>
<td>Study treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>Study Procedures</td>
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<tr>
<td>Height</td>
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</tr>
<tr>
<td>Weight</td>
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<tr>
<td>Vital signs</td>
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</tr>
<tr>
<td>Concomitant medications</td>
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</tr>
<tr>
<td>WHO ordinal assessment</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quality of Life and Functional Status†</td>
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<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Outcomes assessment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X**</td>
</tr>
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</table>
### SOC Laboratory Assessments

<table>
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<tr>
<th>Assessment</th>
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<th>X</th>
<th>X*</th>
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<tbody>
<tr>
<td>Chemistry panel</td>
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<td>X</td>
</tr>
<tr>
<td>CBC with platelet count</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood Group*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PT, PTT if known</td>
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<td></td>
</tr>
<tr>
<td>Anticoagulation Monitoring (e.g., PTT/Antifactor Xa level)**</td>
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<td>X (site-specific)</td>
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</tr>
<tr>
<td>D-dimer***</td>
<td>X</td>
<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Troponin****</td>
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<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Coagulation and inflammatory markers******</td>
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<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Optional Biorepository</td>
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<td></td>
</tr>
</tbody>
</table>

*Blood group taken from hospital record or self report if that is not available.

** Frequency and mode (Anti-factor Xa/aPTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT.

***Baseline D-dimer is strongly recommended (sample should be obtained prior to randomization, and results may need to be available at the time of randomization if the D-dimer value is needed to assess arm-specific eligibility). All values collected should be recorded.

****Strongly recommended as part of routine care.

*****Optional, listed in case report form.

†Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge).

‡or 14 days, whichever is earlier

§Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days, when contacted to ascertain vital status. (Instruments detailed in the manual of operations).

**Participants may be contacted to ascertain vital status.

A May be collected at hospital discharge and at 28 days in participants who remain in hospital at that time.

### A3.4 Potential Risks & Benefits

#### A3.4.1 Known Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots. The therapeutic dose anticoagulation group will receive potent anticoagulation and thus may be at higher risk of bleeding.

#### A3.4.2 Known Potential Benefits

A study from patients with COVID-19 hospitalized in China found that patients with elevated D-dimer had the benefit of prophylactic dose anticoagulation versus no anticoagulation. Thus, there is a direct benefit of decreased clotting events in patients treated with any anticoagulation. The therapeutic dose anticoagulation arm demonstrated superiority to the prophylactic-dose anticoagulation arm in moderate patients in version 1.0 of this study protocol. All participants will be closely monitored by the study team and any changes will be discussed with the treating physicians and/or clinical team. There is a potential direct benefit of identifying clots or bleeding more rapidly.
based on this monitoring. This trial will contribute to the body of generalizable knowledge about the best antithrombotic strategy to use to minimize the risk of clotting in patients with COVID-19.

**A3.5 Study Enrollment**

**A3.5.1 Inclusion Criteria**
Same as the Master Protocol.

Based on the pathophysiology of COVID-19 associated thrombosis, we seek to primarily enroll patients with an elevated D-dimer. It is strongly recommended to enroll patients with a documented D-dimer above the upper limit of normal for the institutional range.

**A3.5.2 Exclusion Criteria**
In addition to the exclusion criteria noted in the master protocol, arm-specific exclusion criteria are as follows:

- Severe illness - requires ICU level of care at the time of randomization (receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)
- Contraindication to anticoagulation, including but not limited to:
  - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
  - known hypersensitivity to any of the study agents
  - known history of an inherited or active acquired bleeding disorder
  - known history of heparin induced thrombocytopenia
  - recent ischemic stroke
  - history of intracranial hemorrhage at any time
- Platelet count < 50x 10⁹/L
- Hemoglobin < 8 g/dL
- Requirement for ASA >162 mg per day that it cannot be stopped safely
- Requirement for P2Y12 inhibitor that cannot be stopped safely

**A3.6 Event Adjudication**
A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

**A3.7 Safety Analyses**
The safety event of importance for the therapeutic dose anticoagulation is major bleeding. The rates of ISTH major bleeding, ICH and fatal bleeds, and mortality will be monitored. For ISTH major bleeding, ICH and fatal bleeds, and all-cause mortality the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

**A3.8 Statistical Analyses**
The therapeutic dose anticoagulation arm demonstrated superiority to the prophylactic-dose anticoagulation arm in moderate patients. This arm is continuing in the trial and will serve as a control arm for efficacy on the primary analysis and the secondary endpoints and safety analyses for additional arms.

The primary Bayesian statistical model (see Appendix 1.3) will be used for modeling this arm in comparing to additional arms. Appendix 1.3 presents the interim analysis schedule and adaptive decision rules.
A3.9 References

Appendix 4: Prophylactic Dose Anticoagulation (Arm B)

Based on DSMB review and NHLBI Determination, as of Jan 21, 2021 patients who are non-ICU level of care at screening/potential enrollment (moderate illness) are NOT eligible for Arm B.

Any of the following strategies are recommended for prophylactic dose anticoagulation:

A4.1 Prophylactic Dose Anticoagulation*

<table>
<thead>
<tr>
<th>CrCl</th>
<th>BMI</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Fondaparinux</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30</td>
<td>&lt;40</td>
<td>40 mg SC q24h</td>
<td>5000 units SC q24h</td>
<td>4500 units SC q24h</td>
<td>2.5 mg SC q24h</td>
<td>5000 units SC q8-12h</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
<td>40 mg SC q12h</td>
<td>5000 units SC q12h</td>
<td>9000 units SC q24h</td>
<td>NA</td>
<td>7500 units SC q8h</td>
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<td>Heparin 5000 units SC q8-12h</td>
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</tr>
<tr>
<td></td>
<td>≥40</td>
<td>Heparin 7500 units SC q8h</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*All drugs are considered standard of care as an anticoagulant. Different drugs are used in different regions, countries, and hospital formularies. As a pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

It is recommended that participants be given prophylactic-dose parenteral anticoagulation daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician.

Full therapeutic dose anticoagulation (therapeutic dose UFH or LMWH) should be used for clinical indications including a thrombotic event, atrial fibrillation, acute coronary syndrome.

If aspirin is to be prescribed, the maximum dose permitted is 162 mg per day. If a P2Y12 was prescribed before randomization, it is stopped at the time of randomization. Note that requirement for P2Y12 inhibitor or for a dose of aspirin greater than 162 mg per day is an exclusion criterion. However, a P2Y12 inhibitor may be used if a clinical indication develops eg, coronary artery stenting. This is not a protocol deviation.

A4.2 Discontinuation of study intervention

Anticoagulation should be discontinued if there is clinical bleeding or another complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time...
possible, but not longer than 24 hours – such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

### A4.3 Study Schedule

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening/Enrollment</th>
<th>Hospital Duration</th>
<th>28 days and/or hospital discharge**</th>
<th>90 days post randomization**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
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<tr>
<td>Demographic and Medical History</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Assessment of Inclusion/Exclusion criteria</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Self-reported race/ethnicity and sex</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test, for women of childbearing potential</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<td><strong>SOC Laboratory Assessments</strong></td>
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<td>Optional Biorepository</td>
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</table>

*Blood group taken from hospital record or self report if that is not available.
** Frequency and mode (Anti-factor Xa/PTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT
- All values collected should be recorded.

****Strongly recommended as part of routine care, all values collected should be recorded

*****Optional, listed in case report form

* Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge)

**or 14 days, whichever is earlier

^Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days, when contacted to ascertain vital status. (Instruments detailed in the manual of operations).

** Participants may be contacted to ascertain vital status. May be collected at hospital discharge and at 28 days in participants who remain in hospital at that time

A4.4 Potential Risks & Benefits

A4.4.1 Known Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots.

A4.4.2 Known Potential Benefits

A study from patients with COVID-19 hospitalized in China found that patients with elevated D-dimer had a benefit of prophylactic dose anticoagulation versus no anticoagulation. Thus, there is a direct benefit of decreased clotting events in patients treated with any anticoagulation. All participants will be closely monitored by the study team and any changes will be discussed with the treating physicians and/or clinical team. There is a potential direct benefit of identifying clots or bleeding more rapidly based on this monitoring. This trial will contribute to the body of generalizable knowledge about the best antithrombotic strategy to use to minimize the risk of clotting in patients with COVID-19.

A4.5 Study Enrollment

A4.5.1 Inclusion Criteria

Same as the Master Protocol.

A4.5.2 Exclusion Criteria

In addition to the exclusion criteria noted in the master protocol, arm-specific exclusion criteria are as follows:

- Moderate illness severity – non-ICU level of care at the time of randomization (not receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)
- Contraindication to anticoagulation, including but not limited to
  - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
  - known hypersensitivity to any of the study agents
  - known history of an inherited or active acquired bleeding disorder
  - known history of heparin induced thrombocytopenia
  - recent ischemic stroke
• Indication for therapeutic anticoagulation in the case that it cannot be stopped safely
• Platelet count < 50x 10^9/L
• Hemoglobin < 8 g/dL
• Requirement for ASA >162mg per day that cannot be stopped safely
• Requirement for P2Y12 inhibitor that cannot be stopped safely

A4.6 Event Adjudication
A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A4.7 Safety Analyses
The safety event of importance for the prophylactic dose anticoagulation is serious thrombotic events. The risk is that with a sub therapeutic dose there may be elevated thrombotic events. The rates of serious thrombotic events and mortality will be monitored. For serious thrombotic events the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A4.8 Statistical Analyses
The comparison of therapeutic to prophylactic dose anticoagulation was stopped due to futility and concern for harm in severely ill patients. This arm is continuing in the trial and will serve as a control arm for efficacy on the primary analysis and the secondary endpoints and safety analyses for additional arms.

The primary Bayesian statistical model (see Appendix 1.3) will be used for modeling this arm in comparing to other arms. Appendix 1.3 presents the interim analysis schedule and adaptive decision rules.

A4.9 References

Appendix 5: ACTIV-4 Blood Sampling – proposed samples and times for sites participating in mechanistic studies and biorepository

The goal of the Mechanistic Studies Center and the Biorepository/Central Lab is to add significant value to the clinical trials by collecting high-quality blood samples for studies aimed at elucidating underlying disease mechanisms and insights into how the therapy modifies these underlying disease processes. A goal is to identify biomarkers that can identify pathological mechanisms, predict outcomes, direct therapy, and/or identify higher-risk patient subpopulations.

A5.1 Inpatient sampling

**Blood collection times for inpatients:**

- Days 0 (time of enrollment), 3, 7 and 14. Samples should be obtained within 24 hours after the assigned time point (example: the day 3 sample should be obtained within 72-96 hours after randomization)
- Samples should be coordinated with clinical lab blood draws when possible.

**Standard samples to be collected & volumes at each time point:**

- Citrate plasma
  - Two 4.5 mL Citrate tubes (BD # 369714)
- EDTA plasma
  - One 10 mL EDTA tube (BD# 366643)
- Serum
  - One 5.0 mL Serum tube (BD # 367814)

**Note 1:** We anticipate that some sites may not be able to collect & process all the samples and time points listed above. We plan to work with those sites to identify more limited time points and/or discard samples that could be collected, processed and sent to the biorepository.

**Note 2:** We anticipate that some high-functioning sites may, in addition to the sample collections noted above, also participate in enhanced collections & studies, which may include:

- Additional blood collection tubes such as:
  - HTI SCAT-144 plasma
  - Paxgene RNA whole blood
  - Cell Prep Tube (CPT)
- Whole blood assays:
  - Viscoelastic assays (thromboelastography or thromboelastometry)
  - Platelet aggregometry
  - Whole blood genomics

A5.2 Sample processing

A detailed Manual of Operations (MOP) will provide instructions to clinical lab and research personnel regarding sample processing including centrifugation, processing, freezing, storing, & shipping samples. Also, the following will be provided: training materials; sample processing kits with prelabeled transport and/or storage vials; sample tracking software; shipping materials.
A5.3 Biorepository/Central Lab

The Biorepository will archive biosamples from the clinical sites, and distribute them to the labs doing ACTIV-4 approved mechanistic studies and other research. If ACTIV-4 biosamples cannot be shipped to the Biorepository for some reason, the information will be captured and used to form a “Virtual Biorepository”, so that those samples can contribute to the mechanistic studies as well.
Appendix 6: Additional data inclusion from other trials merged under ACTIV-4 platform

There are several clinical trials that have been testing safety and efficacy of Arm A and B regimens. Data collected in these trials will be included in the data analysis under this protocol provided that the subjects consented for the data to be shared or a waiver of consent and authorization had been granted by the reviewing IRB. The data will be labeled with subject ID and only include dates which are necessary to assess safety and efficacy endpoint events. All other private health information (PHI) will be removed. The data will be stored at the study coordinating center, University of Pittsburgh, in HIPAA compliant electronic system and only coordinating center staff will have access to the data. The statistical analysis plan will account for this additional data.
Appendix 7: Background and Rationale for Arm C: Prophylactic-dose anticoagulation, plus P2Y12 inhibitor for ICU Level of Care (Severe) Cohort

A7.1 Background and Rationale for Arm C

Analysis of therapeutic vs prophylactic anticoagulation in severely ill patients demonstrated that therapeutic anticoagulation was not superior, and there was a trend toward harm. Therefore prophylactic dose anticoagulation is considered standard of care for severely ill patients at the time of this writing. The number of days with organ support or death over the first 21 days of the index hospitalization remained high despite treatment with prophylactic dose anticoagulants, and bleeding risk was < 2%. Therefore, additional antithrombotic strategies should be tested.

Autopsy and clinical data highlight the potential role of platelets and their precursors in the pathogenesis of COVID-19.1-3 Platelets are shed into circulation by megakaryocytes, and during this process, megakaryocytes distribute their transcriptome into platelets. Once in the circulation, platelets can respond to local and systemic conditions and induce monocyte, macrophage and endothelial cell activation.4-6 Prior to COVID-19, it was described that platelet-viral interactions alter the platelet transcriptome and induce a proinflammatory immune mediated platelet phenotype.7 Consistently, platelets isolated from COVID-19 patients are hyperreactive and have an altered transcriptomic signature compared to disease-free controls.3 Biomarkers of platelet activity are elevated in COVID-19 and are associated with thrombosis and all-cause mortality even after multivariable adjustment. These data suggest that platelets are activated in COVID-19 and represent a therapeutic target for improved clinical outcomes.

A7.2. Eligibility Criteria for Arm C

A7.2.1 Inclusion Criteria for Arm C

Same as the Master Protocol.

A7.2.2 Exclusion Criteria for Arm C

In addition to the exclusion criteria noted in the master protocol, arm-specific exclusion criteria are as follows:

- Moderate illness severity – non-ICU level of care at the time of randomization (not receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)
- Contraindication to anticoagulation (heparin or LMWH) or P2Y12 inhibitor, including but not limited to
  - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
  - known hypersensitivity to any of the study agents
  - known history of an inherited or active acquired bleeding disorder
  - known history of heparin induced thrombocytopenia
  - recent ischemic stroke
  - history of intracranial hemorrhage at any time
- Indication for therapeutic anticoagulation in the case that it cannot be stopped safely
- Platelet count < 50 x 10^9/L
- Hemoglobin < 8 g/dL
- Requirement for ASA >162mg per day that it cannot be stopped safely
- Requirement for P2Y12 inhibitor that cannot be stopped safely
A7.3 Study Agents

Arm C consists of the combination of prophylactic-dose anticoagulation, plus an antiplatelet agent in the P2Y12 inhibitor family.

A7.3.1. Prophylactic Dose Anticoagulation*

Any of the following strategies are recommended for prophylactic dose anticoagulation:

<table>
<thead>
<tr>
<th>CrCl</th>
<th>BMI</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Fondaparinux</th>
<th>Heparin</th>
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</thead>
<tbody>
<tr>
<td>≥30</td>
<td>&lt;40</td>
<td>40 mg SC q24h</td>
<td>5000 units SC q24h</td>
<td>4500 units SC q24h</td>
<td>2.5 mg SC q24h</td>
<td>5000 units SC q8-12h</td>
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<tr>
<td>≥40</td>
<td>≥40</td>
<td>40 mg SC q12h</td>
<td>5000 units SC q12h</td>
<td>9000 units SC q24h</td>
<td>NA</td>
<td>7500 units SC q8h</td>
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<tr>
<td>&lt;30</td>
<td>&lt;40</td>
<td>Heparin 5000 units SC q8-12h</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>≥40</td>
<td>≥40</td>
<td>Heparin 7500 units SC q8h</td>
<td></td>
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</tr>
</tbody>
</table>

*All drugs are considered standard of care as an anticoagulant. Different drugs are used in different regions, countries, and hospital formularies. As a pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

It is recommended that participants be given prophylactic-dose parenteral anticoagulation daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician.

Full therapeutic dose anticoagulation (therapeutic dose UFH or LMWH) should be used for clinical indications including a thrombotic event, atrial fibrillation, acute coronary syndrome.
A7.3.2. P2Y12 Inhibitor

The table shows the preferred dosing for P2Y12 inhibitor treatment. Ticagrelor is the preferred P2Y12 inhibitor, but any of the following strategies are acceptable.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Ticagrelor#</th>
<th>Prasugrel*</th>
<th>Clopidogrel</th>
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<tr>
<td>&lt;75 years</td>
<td>&lt;60 kg</td>
<td>no load: 60 mg BID</td>
<td>no load, 5 mg daily</td>
<td>300 mg load**, then 75 mg daily</td>
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<tr>
<td></td>
<td>≥60 kg</td>
<td>30 mg load**, 10 mg daily</td>
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<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>&lt;60 kg</td>
<td>no load: 60 mg BID</td>
<td>not recommended</td>
<td>300 mg load**, then 75 mg daily</td>
</tr>
<tr>
<td></td>
<td>≥60 kg</td>
<td>30 mg load**, 10 mg daily</td>
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</table>

The preferred P2Y12 inhibitor is ticagrelor, which has a rapid onset of action without the need for a loading dose, unless there is a concern about drug-drug interactions (see Manual of Operations). The 60 mg twice daily dose is recommended. If ticagrelor 60 mg is not available, 90 mg dose, may be used. If ticagrelor is not available or is not preferred locally, prasugrel or clopidogrel may be used, preferably with a loading dose, taking into account relevant drug-drug interactions (see Manual of Operations).

# if a participant will be continued on aspirin in addition the assigned P2Y12 inhibitor, aspirin dose must be ≤100 mg when administered with ticagrelor

* Prasugrel is NOT permitted in anyone with a prior stroke or TIA

**The loading dose is preferred because the average time to therapeutic effect with clopidogrel is 5 days without a loading dose, and for prasugrel is 3 days without a loading dose. A loading dose is not required.

A7.3.3. Participants previously taking aspirin before randomization

Participants taking aspirin before randomization are permitted to continue or stop aspirin therapy at the discretion of the treating physician. If a patient is randomized to Arm C and chronic ASA is continued per MD judgment, the recommended dose is 80-100 mg daily; the dose MUST be ≤100 mg daily when administered with ticagrelor.

A7.4 Duration of treatment

It is recommended that participants be given prophylactic-dose parenteral anticoagulation and a P2Y12 inhibitor daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician. At the time of treatment discontinuation, standard of care antithrombotic prophylaxis should be administered.
A7.5 Discontinuation of study intervention
Anticoagulation and/or P2Y12 inhibitor should be discontinued if there is clinical bleeding or another complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE. If HIT occurs, the P2Y12 inhibitor may be continued, at the discretion of the treating physician, taking into account the platelet count.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible – such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

A7.6 Study Schedule

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening/Enrollment</th>
<th>Hospital Duration</th>
<th>28 days and/or hospital discharge*</th>
<th>90 days post randomization**</th>
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<td>Pregnancy Test, for women of childbearing potential</td>
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<td>Quality of Life and Functional Status†</td>
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<td>CBC with platelet count</td>
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<td>D-dimer***</td>
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<td>Coagulation and inflammatory markers*****</td>
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</table>

*Blood group taken from hospital record or self-report if that is not available.
**Frequency and mode (Anti-factor Xa/PTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT
***Baseline D-dimer is recommended. All values collected should be recorded.
****Strongly recommended as part of routine care, all values collected should be recorded
*****Optional, listed in case report form
*^or 14 days, whichever is earlier
^Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days, when contacted to ascertain vital status. (Instruments detailed in the manual of operations).
+Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge)
++Participants may be contacted to ascertain vital status.
^ May be collected at hospital discharge and at 28 days in participants who remain in hospital at that time

A7.7 Potential Risks & Benefits

A7.7.1 Known Potential Risks
Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots. The prophylactic dose anticoagulation plus P2Y12 inhibitor group will receive both anticoagulation and antiplatelet therapy and thus may be at higher risk of bleeding.

A7.7.2 Known Potential Benefits
Accruing data suggest that platelets are hyperactive in the setting of COVID-19. The platelet transcriptome isolated from hospitalized patients with COVID-19 is more pro-inflammatory than the platelet transcriptome from matched controls without COVID-19. Additionally, biomarkers of platelet activity are correlated with incident thrombosis and all-cause mortality. This arm seeks to test the hypothesis that there is a benefit of antiplatelet therapy in addition to prophylactic dose anticoagulation for decreasing adverse events, including macro and micro-thrombosis. This potential benefit is hypothesized to offset an increase in bleeding risk. All participants will be closely monitored by the study team and any changes in antiplatelet therapy will be discussed with the treating physicians and/or clinical team. There is a potential direct benefit of identifying thrombus or bleeding more rapidly based on close study monitoring. This trial will contribute to the body of generalizable knowledge about the antiplatelet strategy to minimize the risk of thrombus and adverse events in patients with COVID-19.
A7.8 Event Adjudication
A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A7.8 Safety Analyses
The safety events of importance for the prophylactic dose anticoagulation plus P2Y12 inhibitor are serious thrombotic events and bleeding. The rates of serious thrombotic events and mortality will be monitored. The rates of serious thrombotic events will be compared to the prophylactic dose anticoagulation arm, as well as to any additional arms added to the platform trial subsequently. For serious thrombotic events the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

Major bleeding is a safety event of importance for this arm. The rates of ISTH major bleeding, ICH and fatal bleeds, and mortality will be monitored. The rates of bleeding will be compared to the control arm (prophylactic dose anticoagulation, no P2Y12 inhibitor) as well as to additional arms. For ISTH major bleeding, ICH and fatal bleeds, and all-cause mortality the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A7.9 Statistical Analyses
The prophylactic dose anticoagulation arm was demonstrated as a therapeutic advantage compared to therapeutic anticoagulation in severe patients. This arm is testing the potential advantage of adding a P2Y12 to the prophylactic dose anticoagulation. This arm will be compared to the prophylactic dose anticoagulation arm for efficacy on the primary analysis and the secondary endpoints and safety analyses for additional arms.

The primary Bayesian statistical model (see Appendix 1.3) will be used for modeling this arm in comparing to other arms. Appendix 1.3 presents the interim analysis schedule and adaptive decision rules.

A7.13 References

Appendix 8: Therapeutic-dose Anticoagulation, Plus P2Y12 Inhibitor (Arm D) for non-ICU Level of Care (Moderate) Cohort

Based on DSMB review and NHLBI Determination, as of Dec 19, 2020 patients who require ICU level of care at screening/potential enrollment are NOT eligible for Arm D.

Arm D consists of the combination of therapeutic-dose anticoagulation, plus an antiplatelet agent in the P2Y12 inhibitor family.

A8.1 Background and Rationale for Arm D

Analysis of therapeutic vs prophylactic anticoagulation in moderately ill patients demonstrated that therapeutic anticoagulation was superior. Therefore therapeutic dose anticoagulation is considered standard of care for moderately ill patients at the time of this writing. The number of days with organ support or death over the first 21 days of the index hospitalization, remained high despite treatment with therapeutic dose anticoagulants, particularly in certain subsets, and bleeding risk was < 2%. Therefore, additional antithrombotic strategies should be tested.

Autopsy and clinical data highlight the potential role of platelets and their precursors in the pathogenesis of COVID-19. Platelets are shed into circulation by megakaryocytes, and during this process, megakaryocytes distribute their transcriptome into platelets. Once in the circulation, platelets can respond to local and systemic conditions and induce monocyte, macrophage and endothelial cell activation. Prior to COVID-19, it was described that platelet-viral interactions alter the platelet transcriptome and induce a proinflammatory immune mediated platelet phenotype. Consistently, platelets isolated from COVID-19 patients are hyperreactive and have an altered transcriptomic signature compared to disease-free controls. Biomarkers of platelet activity elevated in COVID-19 and are associated with thrombosis and all-cause mortality even after multivariable adjustment. These data suggest that platelets are activated in COVID-19 and represent a therapeutic target for improved clinical outcomes.

A8.2 Arm D Eligibility

A8.2.1 Inclusion Criteria

In addition to the inclusion criteria noted in the master protocol:

D-dimer must be ≥ 2-fold elevated above the upper limit of normal.
If D-dimer is < 2-fold elevated or is missing at baseline the following criteria must be met:
- Age ≥ 60 OR
- If age < 60, 1 or more of the following criteria must be met:
  - Higher O2 requirement (e.g., >2L)
  - History of a comorbid condition:
    - Diabetes mellitus
    - Hypertension
    - Chronic kidney disease (eGFR < 60 mg/dL)
    - Cardiovascular disease e.g., prior MI, known coronary artery disease, heart failure, ejection fraction < 50%
    - BMI ≥ 35 kg/m²
A8.2.2 Exclusion Criteria for Arm D

Exclusion criteria for Arm D include any condition that, in the opinion of the investigator, is associated with a risk of bleeding that precludes use of therapeutic dose anticoagulation, plus P2Y12 inhibitor, including those listed below.

Exclusion Criteria

In addition to the exclusion criteria noted in the master protocol, arm-specific exclusion criteria are as follows:

- Severe illness - requires ICU level of care at the time of randomization (receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)
- Age ≥85
- Contraindication to anticoagulation (heparin or LMWH) or P2Y12 inhibitor, including but not limited to:
  - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
  - known hypersensitivity to any of the study agents
  - known history of an inherited or active acquired bleeding disorder
  - known history of heparin induced thrombocytopenia
  - recent ischemic stroke
  - history of intracranial hemorrhage at any time
- Any condition that, in the opinion of the investigator, is associated with a risk of bleeding that precludes use of therapeutic dose anticoagulation, plus P2Y12 inhibitor. Examples include:
  - Structural cerebrovascular lesion
  - Any history of stroke
  - Recent surgery
  - Severe, uncontrolled hypertension (e.g., BP >185/100)
- Platelet count < 50 x 10^9/L
- Hemoglobin < 8 g/dL
- Indication for P2Y12 inhibitor in the case that it cannot be stopped safely
- Indication for aspirin in the case that aspirin cannot be exchanged for a P2Y12 inhibitor (aspirin must be able to be discontinued if the participant is randomized to Arm D)

A8.3 Study Agents

It is recommended that participants be given therapeutic-dose parenteral anticoagulation and a P2Y12 inhibitor daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician. At the time of treatment discontinuation, standard of care antithrombotic prophylaxis should be administered.

If there is a change in status such that the participant becomes severely ill, continue assigned treatment unless:

a) There are contraindications
b) Clinical judgment leads to a change in dose
Follow up continues through 90 days regardless of the change in status.

**A8.3.1. Therapeutic Dose Anticoagulation**

Any of the following strategies are recommended for therapeutic-dose anticoagulation:

<table>
<thead>
<tr>
<th>CrCl BMI</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30</td>
<td>&lt;40</td>
<td>1 mg/kg SC q12h OR 1.5 mg/kg SC q24h</td>
<td>200 units/kg SC q24h OR 100 units/kg SC q12h</td>
<td>175 units/kg SC q24h</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
<td>1 mg/kg SC q12h</td>
<td>100 units/kg SC q12h</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>&lt;40</td>
<td>Heparin IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Initial bolus dose determined by sites, encouraging use of dosing algorithm designed for treatment of VTE. UFH anti-Xa titration is preferred over aPTT if available because achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19.

Note: Tinzaparin commonly used in Canada
Note: Fondaparinux not advised in this setting due to its long half life

**These drugs are considered standard of care as anticoagulants. Different drugs are used in different regions, countries, and hospital formularies. In this pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

A8.3.2. P2Y12 Inhibitor

The table shows the preferred dosing for P2Y12 inhibitor treatment. Ticagrelor is the preferred P2Y12 inhibitor, but any of the following strategies are acceptable.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Ticagrelor</th>
<th>Prasugrel*</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75 years</td>
<td>&lt;60 kg</td>
<td>no load; 60 mg BID#</td>
<td>no load; 5 mg daily</td>
<td>300 mg load**, then 75 mg daily</td>
</tr>
<tr>
<td></td>
<td>≥60 kg</td>
<td></td>
<td>30 mg load**; 10 mg daily</td>
<td></td>
</tr>
<tr>
<td>75-85 years</td>
<td>&lt;60 kg</td>
<td>no load; 60 mg BID#</td>
<td>not recommended</td>
<td>300 mg load**, then 75 mg daily</td>
</tr>
<tr>
<td></td>
<td>≥60 kg</td>
<td></td>
<td>no load; 5 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

The preferred P2Y12 inhibitor is ticagrelor, which has a rapid onset of action without the need for a loading dose, unless there is a concern about drug-drug interactions (see Manual of Operations). The 60 mg twice daily dose is recommended*. *If ticagrelor 60 mg is not available, 90 mg dose, may be used. If ticagrelor is not available or is not preferred locally, prasugrel or clopidogrel may be used, taking into account relevant drug-drug interactions (see Manual of Operations).

* Prasugrel is NOT permitted in anyone with a prior stroke or TIA
**The loading dose is preferred because the average time to therapeutic effect with clopidogrel is 5 days without a loading dose, and for prasugrel is 3 days without a loading dose. A loading dose is not required.**

**A8.3.3. Participants previously taking aspirin before randomization**
Aspirin may not be used in arm D.

**A8.4 Discontinuation of study intervention:**
Patients randomized based on suspicion of COVID-19 whose tests do not confirm SARS-CoV-2 infection should not continue to receive study assigned therapeutic dose anticoagulation, plus P2Y12 inhibitor.

Anticoagulation and/or P2Y12 inhibitor should be discontinued if there is clinical bleeding or other complications sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. The use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE. If HIT occurs, the P2Y12 inhibitor may be continued, at the discretion of the treating physician, taking into account the platelet count.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, such as to allow surgical or other procedures is not a protocol deviation.

If there is a change in status such that the participant becomes severely ill, continue assigned treatment unless:

a) There are contraindications
b) Clinical judgment leads to a change in dose

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

**A8.5 Study Schedule**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening/Enrollment</th>
<th>Hospital Duration</th>
<th>28 days and/or hospital discharge*</th>
<th>90 days post randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic and Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of Inclusion/Exclusion criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported race/ethnicity and sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test, for women of childbearing potential</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study Procedures

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>X*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
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<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WHO ordinal assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quality of Life and Functional Status assessment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Outcomes assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>SOC Laboratory Assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry panel</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with platelet count</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood Group*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PT, PTT if known</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation Monitoring (e.g., PTT/Antifactor Xa level)**</td>
<td>X</td>
<td>X (site-specific)</td>
</tr>
<tr>
<td>D-dimer***</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Troponin****</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Coagulation and inflammatory markers*****</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Optional Biorepository</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Blood group taken from hospital record or self report if that is not available.

** Frequency and mode (Anti-factor Xa/aPTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT.

***Baseline D-dimer is strongly recommended (sample should be obtained prior to randomization and results may need to be available at the time of randomization if the d-dimer value is needed to assess arm-specific eligibility). All values collected should be recorded.

****Strongly recommended as part of routine care.

***** Optional, listed in case report form.

^or 14 days, whichever is earlier.

*Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days, when contacted to ascertain vital status. (Instruments detailed in the manual of operations).

*Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge).

**Participants may be contacted to ascertain vital status.

^ May be collected at hospital discharge and at 28 days in participants who remain in hospital at that time.

### A8.6 Potential Risks & Benefits

#### A8.6.1 Known Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots. The therapeutic dose anticoagulation, plus P2Y12 inhibitor group will receive potent anticoagulation and antiplatelet therapy and thus may be at higher risk of bleeding.
A8.6.2 Known Potential Benefits

Accruing data suggest that platelets are hyperactive in the setting of COVID-19. The platelet transcriptome isolated from hospitalized patients with COVID-19 is more pro-thrombotic and more pro-inflammatory than the platelet transcriptome from matched controls without COVID-19. Additionally, biomarkers of platelet activity are correlated with incident thrombosis and all-cause mortality. This arm seeks to test the hypothesis that there is a benefit of antiplatelet therapy in addition to therapeutic dose anticoagulation for decreasing adverse events, including macro and micro-vascular thrombosis. This potential benefit is hypothesized to offset an increase in bleeding risk in this subset of the trial population at lower risk for bleeding. All participants will be closely monitored by the study team and any changes in antiplatelet therapy will be discussed with the treating physicians and/or clinical team. There is a potential direct benefit of identifying thrombus or bleeding more rapidly based on close study monitoring. This trial will contribute to the body of generalizable knowledge about the antiplatelet strategy to minimize the risk of thrombus and adverse events in patients with COVID-19.

A8.7 Event Adjudication

A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A8.8 Safety Analyses

The safety event of importance for the therapeutic dose anticoagulation, plus P2Y12 inhibitor arm is major bleeding. The rates of ISTH major bleeding, ICH and fatal bleeding events, and mortality will be monitored. The rates of bleeding will be compared to the other arms. For ISTH major bleeding, ICH and fatal bleeding events, and all-cause mortality the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A8.9 Statistical Analyses

The therapeutic dose anticoagulation arm was demonstrated as superior to the prophylactic dose anticoagulation in moderate patients. This arm is testing the potential advantage of adding a P2Y12 to the therapeutic dose anticoagulation. This arm will be compared to the therapeutic dose anticoagulation arm without P2Y12 (Arm A) for efficacy on the primary analysis and the secondary endpoints and safety analyses for additional arms.

The primary Bayesian statistical model (see Appendix 1.3) will be used for modeling this arm in comparing to other arms. Appendix 1.3 presents the interim analysis schedule and adaptive decision rules.

A8.10 References


