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

Supported by:
National Heart Lung and Blood Institutes (NHLBI), National Institute of Neurological Disorders (NINDS), ACTIV (ACTIV IV), National Institutes of Health (NIH), Biomedical Advanced Research and Development Authority (BARDA), Operation Warp Speed (OWS), U.S. Department of Health & Human Services (HHS)

Version Number: 1.0

21AUG2020

Trial Chair	Judith Hochman, MD Harold Snyder Family Professor & Associate Director of Cardiology Senior Associate Dean for Clinical Sciences Co-Director, NYU-HHC Clinical and Translational Science Institute NYU School of Medicine 530 First Avenue, Skirball 9R New York, NY 10016 Tel 212-263-6927 Email: judith.hochman@nyumc.org
Coordinating Center	Stephen Wisniewski, PhD Professor of Epidemiology Vice Provost for Budget and Analytics University of Pittsburgh Email: STEVEWIS@pitt.edu Matthew Neal, MD Roberta G. Simmons Assistant Professor of Surgery Attending Surgeon, Division of Trauma and Acute Care Surgery Assistant Professor of Clinical and Translational Science and Critical Care Medicine Departments of Surgery, Critical Care Medicine, and the Clinical and Translational Science Institute (CTSI), University of Pittsburgh University of Pittsburgh Medical Center F1271.2 PUH 200 Lothrop Street Pittsburgh, PA 15213 Tel: 412-647-1158 Fax: 412-647-1448 Email: nealm2@upmc.edu
Trial Biostatisticians	Scott Berry, PhD President, Senior Statistical Scientist Berry Consultants Tel 979-575-6280 Email scott@berryconsultants.com Eric Leifer, PhD NHLBI leifere@nhlbi.nih.gov << >>
NHLBI Representative	Andrei Kindzelski, MD kindzleskial@nhlbi.nih.gov
HHS Representative	Rachel Harrigan Rachel.Harrigan@hhs.gov
IND	Waiver
ClinicalTrials.gov Identifier	NCT04505774

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: Aug. 2020

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

_____

Name of Facility

_____

Location of Facility (City, Country)

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome.
AT	Arterial Thrombosis
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CrCl	Creatinine Clearance
COVID-19	Coronavirus Disease
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DIC	Disseminated Intravascular Coagulation
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
ECMO	Extracorporeal Membrane Oxygenation
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GI	Gastrointestinal
HFNO	High-flow (≥30L/min) Nasal Oxygen
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to Treat
KDIGO	Kidney Disease Improving Global Outcomes
LAR	Legally Authorized Representative

LOS	Length of Stay
MI	Myocardial Infarction
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
NIV	Non-invasive ventilation
OHRP	Office for Human Research Protections
OHSR	Office of Human Participants Research
OSFD	Organ Support Free Days
PE	Pulmonary Embolism
PI	Principal Investigator
PRBC	Packed Red Blood Cells
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
sICH	Symptomatic Intracranial or Intracerebral Hemorrhage
SOC	Standard of Care
SOP	Standard Operating Procedure
US	United States
VTE	Venous thromboembolism
WHO	World Health Organization

Master Protocol Summary

Title	A Multicenter, Adaptive, Randomized, Open Label Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19
Short Title	ACTIV-4 ACUTE
Brief Summary	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
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 under-represented 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.

Statistical Analysis	Inferences in this trial are based on a Bayesian statistical model, which considers the variation in outcomes by site, disease state, time, and arm of the trial. The specific analyses for each arm, including interim analysis schedule, are specified in each arm-specific appendix.

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%) (1). 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) (2). 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 pre-determined statistical thresholds as defined in the arm-specific appendix (Appendix 3 and 4). Each arm will have an adaptive component for determinations of futility or success.

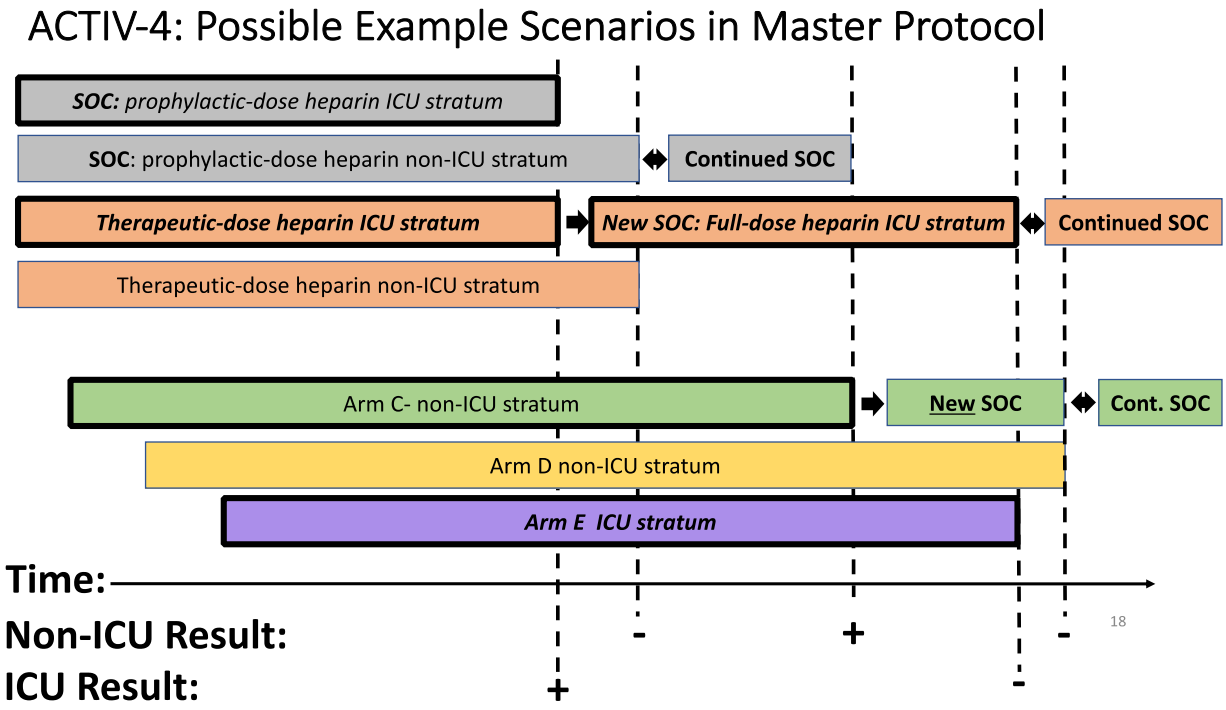
1.2 *Potential Risks & Benefits*

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 All-cause mortality at 90 days 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:

- ≥ 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 SARSCoV2 with a positive microbiological test prior to randomization. At centers where there is 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.

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; See 7.4.7)
- Demonstration of efficacy or lack thereof that would warrant stopping (See 7.4.7)
- 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*

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge*** **	**90-days post randomization**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and gender	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			

Weight	X			
Vital signs	X			
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Outcomes Assessment		X	X	X
SOC Laboratory Assessments				
Chemistry panel	X	X		
Hematology panel	X	X		
See arm-specific appendix for additional measures				
D-dimer*	X			
Blood Group**	X			

*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 $Y_i = \{-1, 0, 1, \ldots, 21, 22\}$ 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. The generic primary analysis model is formulated as follows:

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

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 ≤ 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 $\alpha_{y,subtype}$ 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 β_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 β parameters model any covariate effects included in the model. The λ 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 10 patients weight on real-world evidence-based outcomes (details in the SAP).

$$logit(\alpha_{y,s}) \sim Dirichlet(10 * P), where \ldots$$

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

$$\nu_{Site,s} \sim N(\mu_{country,s}, \tau^2_{country,s}), site = 2, \ldots, N_{Site}$$

$$\mu_{country,s} \sim N(0,1);\ \tau^2_{country,s} \sim IG(0.25,0.1), s = 1,2$$

A referent site, expected to be the largest enrolling site, will be set such that $\nu_{Site} \equiv 0$. 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:

$$\lambda_1 = \lambda_2 \equiv 0$$

$$\lambda_3 \sim N(0,0.15^2)$$

$$\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0, \tau^2_{Time}), T \geq 4$$

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:

$$\theta_{1,subtype,d} \equiv 0$$

The effect of each other arm introduced will be modeled hierarchically across disease subtype and d-dimer level. The treatment effects for each arm, *a*, are modeled as:

$$\theta_{a,s:d} \sim N(\mu_a, \tau^2_a), s{:}\, d = 1{:}\,1, 1{:}\,2\ ,2, \qquad a = 1, \ldots, N_{arms}$$

$$\mu_a \sim N(0,1);\ \tau^2_a \sim IG(0.25,0.1) \text{ (TBD)}$$

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, θ, 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:

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

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 (δ), 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.

The following figure presents the assumptions for the ordinal outcome of organ-support free days for the control arm and the distribution under each assumed treatment effect for the cumulative

odds-ratio used for these power calculations. The second figure presents the power for each assumed effect size for each fixed sample size (the x-axis is the total number on the two arms).

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).

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 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.

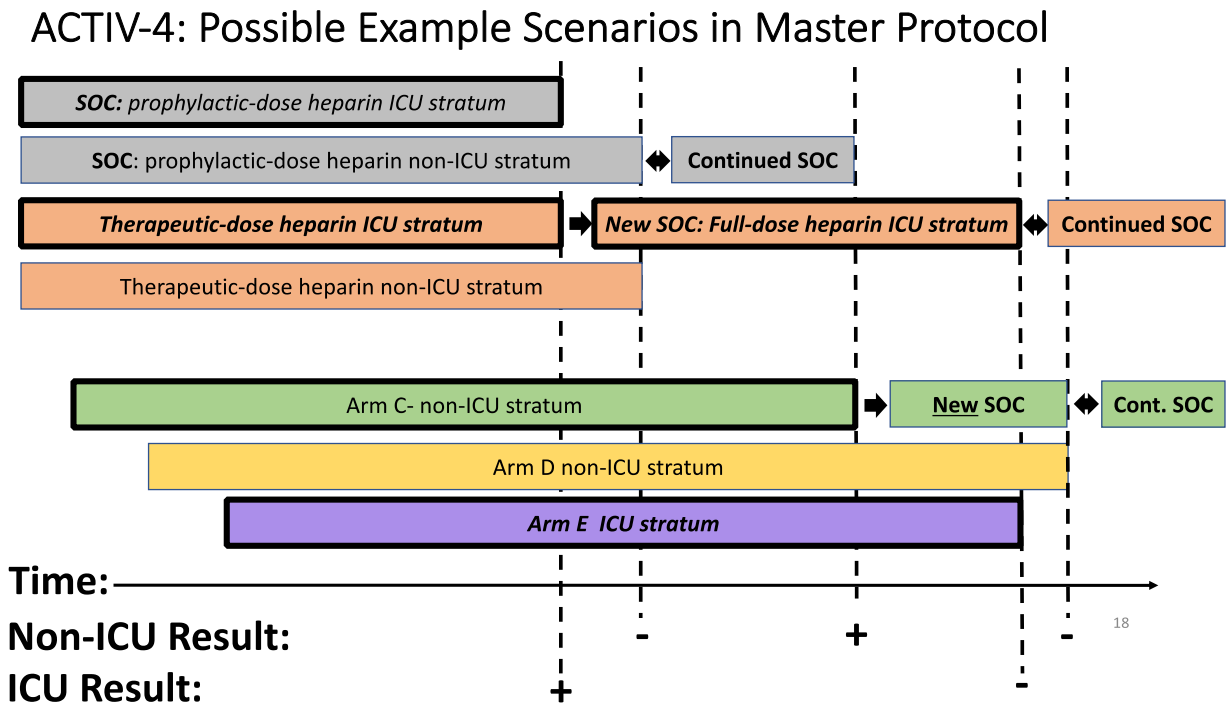
17 References

1. Bikdeli, B., et al., COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol, 2020. 75(23): p. 2950-2973.
2. Klok, F.A., et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res, 2020. 191: p. 145-147.
3. Middeldorp, S., et al., Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost, 2020.

4. Poissy, J., et al., Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. Circulation, 2020.
5. Zhou, F., et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 2020. 395(10229): p. 1054-1062.
6. Tang, N., et al., Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost, 2020. 18(5): p. 1094-1099.
7. Xu J, W.L., Zhao L, et al. , Risk assessment of venous thromboembolism and bleeding in COVID-19 patients. BMC Pulmonary Medicine 2020.
8. Danzi, G.B., et al., Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J, 2020. 41(19): p. 1858.
9. Xie Y, W.X., Yang P, Zhang S, COVID-19 complicated by Acute Pulmonary Embolism. Radiology: Cardiothoracic Imaging, 2020. 2(2):e200067.
10. Beristain-Covarrubias, N., et al., Understanding Infection-Induced Thrombosis: Lessons Learned From Animal Models. Front Immunol, 2019. 10: p. 2569.
11. Clayton, T.C., M. Gaskin, and T.W. Meade, Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. Int J Epidemiol, 2011. 40(3): p. 819-27.
12. Goeijenbier, M., et al., Review: Viral infections and mechanisms of thrombosis and bleeding. J Med Virol, 2012. 84(10): p. 1680-96.
13. Smeeth, L., et al., Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet, 2006. 367(9516): p. 1075-1079.
14. Harms, P.W., et al., Autopsy findings in eight patients with fatal H1N1 influenza. Am J Clin Pathol, 2010. 134(1): p. 27-35.
15. Kwong, J.C., et al., Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med, 2018. 378(4): p. 345-353.
16. Wong, R.S., et al., Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. BMJ, 2003. 326(7403): p. 1358-62.
17. Obi, A.T., et al., Empirical systemic anticoagulation is associated with decreased venous thromboembolism in critically ill influenza A H1N1 acute respiratory distress syndrome patients. J Vasc Surg Venous Lymphat Disord, 2019. 7(3): p. 317-324.
18. Rapkiewicz, A., et al, Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in 4 COVID-19: a case series. Lancet EClinical Medicine, 2020, in press.
19. Oxley, T.J., et al., Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med, 2020. 382(20): p. e60.
20. Al-Samkari, et al., COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. Blood, 2020. Online ahead of print.
21. Centers for Disease Control and Prevention. COVID-19 in Racial and Ethnic Minority Groups. 2020.
22. Price-Haywood EG, Burton J, Fort D and Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. *N Engl J Med*. 2020.
23. Robert W. Aldridge, Dan Lewer, Srinivasa Vittal Katikireddi, Rohini Mathur, Neha Pathak, Rachel Burns, Ellen B. Fragaszy, Anne M. Johnson, Delan Devakumar, Ibrahim Abubakar and Haywar A. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data [version 1; peer review: 3 approved with reservations]. *Wellcome Open Res*. 2020;5.
24. Niedzwiedz CL, O'Donnell CA, Jani BD, Demou E, Ho FK, Celis-Morales C, Nicholl BI, Mair FS, Welsh P, Sattar N, Pell JP and Katikireddi SV. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. *BMC Med*. 2020;18:160.

25. Millett GA, Jones AT, Benkeser D, Baral S, Mercer L, Beyrer C, Honermann B, Lankiewicz E, Mena L, Crowley JS, Sherwood J and Sullivan P. Assessing Differential Impacts of COVID-19 on Black Communities. *Ann Epidemiol*. 2020.
26. Kamin-Mukaz D, Gergi M, Koh I, Zakai NA, Judd SE, Sholzberg M, Bauman Kreuziger L, Freeman K, Colovos C, Cushman M. Biomarkers of COVID-19 coagulopathy and D-dimer in a biracial cohort study [abstract]. Res Pract Thromb Haemost 2020;4:Suppl2.

Appendix 1: Criteria for Addition and Replacement of Arms



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 30 to 60 liters per minute (but may be as low as 20 liters per minute) 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.
- A patient must be extubated and not receiving mechanical ventilation for at least 2 days before being considered free of mechanical ventilation. If a patient was extubated and re-intubated and placed back on mechanical ventilation within 1 or 2 days, the patient is considered to be on mechanical ventilation during those 1 or 2 days before re-intubation.
- 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 vent 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

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, rarely- epidural hematoma, spinal hematoma. Secondary hemorrhagic stroke: Ischemic infarct containing blood - often subclassified by size- PH1, PH2, PH3.

ICU Level of care disease state

Defined as planned admission to ICU or receipt of organ support as defined in the 21-day organ support free days.

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

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

WHO ordinal scale for clinical improvement (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

Patient State	Score	Descriptor
Uninfected	0	No clinical or virological evidence of infection
Ambulatory	1	No limitation of activities
	2	Symptomatic: Limitation of activities
Hospitalized: Mild disease	3	Hospitalized; no oxygen therapy
	4	Hospitalized; oxygen by mask or nasal prongs
Hospitalized: Severe disease	5	Non-invasive ventilation or high-flow oxygen
	6	Intubation & Mechanical ventilation
	7	Ventilation and additional organ support – pressors, RRT, ECMO
Death	8	Death

Appendix 3: Therapeutic-dose Anticoagulation (Arm A)

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

*A3.1 Therapeutic Dose Anticoagulation***

<table>
<tr><th>CrCl</th><th>BMI</th><th>Enoxaparin</th><th>Dalteparin</th><th>Tinzaparin</th><th>Heparin</th></tr>
<tr><td rowspan="2">≥30</td><td><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 rowspan="2">175 units/kg SC q24h</td><td rowspan="2">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>1 mg/kg SC q12h</td><td>100 units/kg SC q12h</td></tr>
<tr><td rowspan="2"><30</td><td><40</td><td colspan="4" rowspan="2">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></tr>
</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 anticoagulants (1). 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 there is transfer to ICU level care, continue assigned treatment unless there are contraindications.

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

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge+**	**90 days post randomization**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Outcomes assessment		X	X	X++
SOC Laboratory Assessments				
Chemistry panel	X	X	X^	
CBC with platelet count	X	X	X^	
Blood Group*	X			
PT, PTT if known	X	X		
Anticoagulation Monitoring (e.g., PTT/ Antifactor Xa level)**	X	X (site-specific)		
D-dimer***	X	X	X^	
Troponin****	X	X	X^	
Coagulation and inflammatory markers*****	X	X	X^	
Optional Biorepository	X	X		

*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 required with SOC labs (sample needs to be obtained prior to randomization, but results do not need to be available at the time of randomization). 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)
[++]Participants will be contacted to ascertain vital status.functional status and quality of life. (Instruments detailed in the manual of operations)
^ 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 recent 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 both arms – although this trial hypothesizes that the benefit in terms of decreasing adverse events will be superior in this therapeutic dose 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 anticoagulation 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.

A3.5.2 Exclusion Criteria

Exclusion criteria are as follows:

- Contraindication to anticoagulation, including but not limited to:
    - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
    - 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
- Platelet count < 50x 10^9/L
- Hemoglobin < 8 g/dL
- Pregnancy
- Patient on dual antiplatelet therapy, when one of the agents 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. The rates of bleeding will be directly compared to the control arm (prophylactic dose anticoagulation) as well as to any additional arms added to the platform trial subsequently if this arm continues. 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 will be compared to the control arm (prophylactic dose anticoagulation) for efficacy on the primary analysis and the secondary endpoints. In addition, this arm will be compared to the control and may be stopped for futility if it does not improve the primary clinical outcome.

The primary Bayesian statistical model (see Master protocol) will be used for modeling this arm.

A3.8.1 Interim Analysis Schedule

Interim analyses will take place for this arm starting when 200 participants have been randomized to this arm and have 21-day follow-up. Analyses will continue with every 200 participants enrolled to this arm, at sample sizes of 400, 600, 800, and 1,000.

A3.9 *Adaptive Decision Rules*

At each analysis the following rules will be carried out:

1. **Superiority**: Within each subtype, if the posterior probability of superiority of the therapeutic dose anticoagulation arm compared to the prophylactic dose (control) anticoagulation arm is greater than 0.99, then the therapeutic dose anticoagulation arm will be declared superior to prophylactic dose anticoagulation in that subtype. If the prophylactic dose anticoagulation arm has not been discontinued in that disease subtype, then this result trigger should discontinue randomization within that stratum to the prophylactic dose anticoagulation arm.

If the therapeutic dose anticoagulation arm reaches 1,000 total participants enrolled without a declaration of superiority or futility within a subtype, this arm may be discontinued within these remaining subtypes. If the steering committee decides it is important to keep this arm in the platform trial, it may expand beyond this 1,000 participants randomized and this plan will be amended.

A3.10 *Operating Characteristics*

See Arm-specific SAP for the operating characteristics for the therapeutic dose anticoagulation arm.

A3.11 References

1. Garcia D, Baglin T, Weitz J, et al. Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e24S–e43S.

Appendix 4: Prophylactic Dose Anticoagulation (Arm B)

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

A4.1 *Prophylactic Dose Anticoagulation**

CrCl	BMI	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux	Heparin
≥30	<40	40 mg SC q24h	5000 units SC q24h	4500 units SC q24h	2.5 mg SC q24h	5000 units SC q8-12h
	≥40	40 mg SC q12h	5000 units SC q12h	9000 units SC q24h	NA	7500 units SC q8h
<30	<40	Heparin 5000 units SC q8-12h				
	≥40	Heparin 7500 units SC q8h				

*All drugs are considered standard of care as an anticoagulant (1–2). 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.

The following measures are recommended during CRRT: regional citrate, heparin priming and prophylactic dose heparin administration (without measurable systemic anticoagulation)

Full therapeutic dose anticoagulation (therapeutic dose UFH or LMWH) is permitted as rescue therapy in the event of suspected or confirmed deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, acute coronary syndrome, circuit or line thrombosis during continuous renal replacement therapy (despite regional measures) or sustained low-efficiency daily dialysis. Full therapeutic dose anticoagulation is also acceptable for intermittent hemodialysis. These are adherent to protocol. Full therapeutic anticoagulation is not recommended solely for clinical deterioration involving transfer to ICU-level care in this setting in the absence of suspected PE. If the team changes to therapeutic dose for other reasons (e.g., increasing D-dimer; team is not comfortable with prophylactic dose, minor increase in oxygen support), then this is not adherent to protocol and site PI will need to discuss this with the clinical team.

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*

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge[+]**	**90 days post randomization[++]**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X^	X
Outcomes assessment		X	X	X[++]
SOC Laboratory Assessments				
Chemistry panel	X	X	X^	
CBC with platelet count	X	X	X^	
Blood Group*	X			
PT, PTT if known	X	X		
Anticoagulation Monitoring (ex, PTT/ Antifactor Xa level)**	X	X (site-specific)		
D-dimer***	X	X	X^	
Troponin****	X	X	X^	
Coagulation and inflammatory markers*****	X	X	X^	
Optional Biorepository	X	X		

*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 required with SOC labs (sample needs to be obtained prior to randomization, but results do not need to be available at the time of randomization). 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)

[++]Participants will be contacted to ascertain vital status and functional status and quality of life. (Instruments detailed in the manual of operations)

^ 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 recent 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 both arms – although this trial hypothesizes that the benefit in terms of decreasing adverse events will be superior in this therapeutic dose 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 anticoagulation 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

Exclusion criteria are as follows:

- Contraindication to anticoagulation, including but not limited to
    - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
    - known history of a bleeding disorder 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

- Pregnancy
- Patient on dual antiplatelet therapy when one of the agents 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. The rates of serious thrombotic events will be directly compared to the therapeutic dose anticoagulation arm as well as to any additional arms added to the platform trial subsequently if this arm continues. 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 prophylactic anticoagulation arm is intended as the initial control arm in the platform trial. This arm will be the referent arm in the Bayesian statistical model. This arm will not have any efficacy or futility stopping rules. This arm will function as a comparator within each of the subtypes and will continue in each until an arm demonstrates efficacy compared to this arm and it is discontinued in that subtype. This prophylactic dose anticoagulation arm is likely to be the safest of the arms in this platform trial and hence arms will have a need to demonstrate statistical superiority to this arm for it to be discontinued.

A4.9 Number of Participants

Approximately 1,000 participants will be randomized to this arm and have 90-day follow-up.

A4.10 References

1. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 suppl):e227S-277S.

2. Garcia D, Baglin T, Weitz J, et al. Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e24S–e43S.

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 1 (time of enrollment), 3, 7 and 14
- 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.

A5.4 References

1. Bikdeli B, Madhavan MV, Jimenez D et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:2950-2973.
2. Klok FA, Kruip M, van der Meer NJM et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-147.
3. Middeldorp S, Coppens M, van Haaps TF et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020.
4. Poissy J, Goutay J, Caplan M et al. Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. Circulation 2020.
5. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
6. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA.
7. Xu J WL, Zhao L, et al. . Risk assessment of venous thromboembolism and bleeding in COVID-19 patients. BMC Pulmonary Medicine 2020.
8. Rapkiewicz A, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in 4 COVID-19: a case series. Lancet EClinical Medicine 2020.
9. Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP, Cunningham AF. Understanding Infection-Induced Thrombosis: Lessons Learned From Animal Models. Front Immunol 2019;10:2569.
10. Clayton TC, Gaskin M, Meade TW. Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. Int J Epidemiol 2011;40:819-27.
11. Goeijenbier M, van Wissen M, van de Weg C et al. Review: Viral infections and mechanisms of thrombosis and bleeding. J Med Virol 2012;84:1680-96.
12. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006;367:1075-1079.
13. Harms PW, Schmidt LA, Smith LB et al. Autopsy findings in eight patients with fatal H1N1 influenza. Am J Clin Pathol 2010;134:27-35.
14. Kwong JC, Schwartz KL, Campitelli MA et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med 2018;378:345-353.
15. Wong RS, Wu A, To KF et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. BMJ 2003;326:1358-62.
16. Obi AT, Tignanelli CJ, Jacobs BN et al. Empirical systemic anticoagulation is associated with decreased venous thromboembolism in critically ill influenza A H1N1 acute respiratory distress syndrome patients. J Vasc Surg Venous Lymphat Disord 2019;7:317-324.
17. Oxley TJ, Mocco J, Majidi S et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020;382:e60.
18. Manne BK, Denorme F, Middleton EA et al. Platelet Gene Expression and Function in COVID-19 Patients. Blood 2020.
19. Berger C, Fiorelli M, Steiner T et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? Stroke 2001;32:1330-5.

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 regiments. 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 Pittsburg, 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.