COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis

Short Title: COVID-19 Post-hospital Thrombosis Prevention Study

A multicenter, adaptive, prospective, randomized trial evaluating the efficacy and safety of antithrombotic strategies in patients with COVID-19 following hospital discharge

ClinicalTrials.gov Number: NCT04650087

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

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Statement of Compliance

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 Harmonization ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. 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, and ICH E6(R2) GCP guidelines.

Site Investigator Signature:

Signed:_____ Date: _____

Name and Title

List of Abbreviations

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AE	Adverse Event
COVID-19	Coronavirus Disease
CRF	Case Report Form
CRNMB	Clinically Relevant non-Major Bleeding
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DIC	Disseminated intravascular coagulation
DOAC	Direct oral anticoagulant
DSMB	Data and Safety Monitoring Board
DVT	Deep Venous Thrombosis
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICU	Intensive Care Unit
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to Treat
LAR	Legally Authorized Representative
LMWH	Low Molecular Weight Heparin
MOP	Manual of Procedures
NIH	National Institutes of Health
PE	Pulmonary Embolism
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
VTE	Venous thromboembolism
WHO	World Health Organization

Master Protocol Summary

Title	**COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis** A multicenter, adaptive, prospective, randomized trial evaluating the efficacy and safety of antithrombotic strategies in patients with COVID-19 following hospital discharge
Short Title	**COVID-19 Post-hospital Thrombosis Prevention Study**
Brief Summary	This study is an adaptive, prospective, randomized trial designed to compare the effectiveness and safety of antithrombotic therapy with no antithrombotic therapy after hospitalization for 48 hours or longer for COVID-19. For Stage 1 of this study, participants will be randomized to either prophylactic anticoagulation or no anticoagulant therapy for 30 days, and then followed for an additional 60 days after the completion of treatment (total duration of follow-up, approximately 90 days). Biobanking of samples for future biomarker and mechanistic studies will be available for centers able to participate and collect samples from eligible participants. Samples will be collected at the time of enrollment and after the completion of 30 days of therapy
Objectives	1. Primary Objective: To determine the most effective and safe antithrombotic strategy to prevent the composite outcome of symptomatic deep vein thrombosis, pulmonary embolism, other venous thromboembolism, ischemic stroke, myocardial infarction, other arterial thromboembolism, and all-cause mortality by 30 days following discharge from the hospital. 2. Secondary Objectives: To determine the most effective and safe antithrombotic strategy on (1) the endpoint of venous thromboembolism (inclusive of symptomatic deep vein thrombosis, pulmonary embolism, other venous thromboembolism) by 30 days in the study population; (2) the endpoint of arterial thromboembolism (inclusive of ischemic stroke, myocardial infarction, other arterial thromboembolism) by 30 days in the study population; and (3) the composite primary outcome by 45 and 90 days following discharge from the hospital 3. To establish a repository of biospecimens collected at the time of enrollment and after completion of therapy.
Methodology	Adaptive, prospective, randomized controlled trial

Endpoint	Primary Endpoint: First occurrence of any of the components of the composite endpoint of symptomatic deep vein thrombosis, pulmonary embolism, other venous thromboembolism, ischemic stroke, myocardial infarction, other arterial thromboembolism, and all-cause mortality by 30 days post-discharge from the hospital Secondary Endpoints: (1) Venous thromboembolism (inclusive of symptomatic DVT of the upper or lower extremities, symptomatic and/or clinically relevant PE, and other symptomatic venous thrombosis, including cerebral sinus and splanchnic vein thrombosis) by 30 days post-discharge from the hospital; (2) Arterial thromboembolism (inclusive of symptomatic ischemic stroke, myocardial infarction, and other symptomatic arterial thromboembolic events) by 30 days post-discharge from the hospital; and (3) the composite primary endpoint by 45 days and 90 days post-discharge from the hospital Primary Safety Endpoints: Major bleeding, as defined by the ISTH; clinically-relevant non-major bleeding
Study Duration	At least one year
Participant Duration	Approximately 90 days from randomization
Duration of assigned treatment strategy	30 days for the primary outcome in Stage 1.
Population	Adults ≥ 18 years of age with COVID-19 who are hospitalized for 48 hours or longer and who are ready for discharge from the hospital
Key exclusion criteria	1. Clinical requirement for anticoagulant therapy (therapeutic dose or prophylactic dose) 2. Contraindication to anticoagulant therapy 3. Anticipated life-expectancy < 90 days
Study Sites	Up to 400 sites
Number of participants	The estimated sample size (for Stage 1) is 2,660 participants per Study Arm based on an estimated baseline rate of the primary endpoint of ~4%.

Description of Study Agents (Stage 1)	Stage 1 is a two-arm trial incorporating: 1. Prophylactic dose anticoagulant therapy 2. Matching placebo Participants will be enrolled prior to discharge from the hospital, randomized as close to time of discharge as possible, and will begin the study medication (either prophylactic anticoagulation or matching placebo) upon discharge from the hospital for a total of 30 days. Study participants will be stratified based on: (1) whether or not they are taking an antiplatelet agent (e.g., aspirin, clopidogrel); and (2) on their WHO ordinal scale score dichotomized (below five vs. five or above). Subsequent stages may investigate alternative antithrombotic strategies or focus on selected high-risk patient subsets.
Key Procedures	See arm-specific Appendices
Statistical Analysis	A frequentist approach has been used for the sample size calculations. Interim analyses will be used to guide decisions about stopping based on efficacy and futility. The primary analyses will be based on intention-to-treat approaches.

1. Introduction, Background Information and Scientific Rationale

1.1 *Background Information, Significance and Relevant Literature*

In December 2019, an outbreak of pneumonia of unknown cause was first observed in Wuhan, the capital of Hubei province in China. By early January, a novel coronavirus was isolated from these patients, referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and initial descriptive clinical reports of the pandemic designated coronavirus disease 2019 (COVID-2019) by the World Health Organization (WHO) began to appear shortly afterwards (1). The disease has spread explosively, and, by early July 2020, about 7 months from the initial reports, more than 11 million people worldwide had been confirmed to have a COVID-19 infection, with more than 530,000 deaths. In addition to the healthcare problems associated with this coronavirus, it has resulted in worldwide disruption of everyday life as measures have been introduced to interfere with the rapid spread of the virus and treat those patients with the infection.

The clinical manifestations associated with COVID-19 range from asymptomatic infections through severe pneumonia and death. A significant inflammatory response is frequently seen in patients who require hospitalization, associated with dramatic elevations in inflammatory biomarkers such as the ESR and CRP, as well as proinflammatory cytokines such as IL6 and others. This robust inflammatory response is also associated with elevated fibrinogen levels, as well as increased levels of D-dimers, even at initial presentation to the hospital (2). Notably, elevated D-dimer levels were associated with increased mortality (2, 3), although it was also noted that these patients were not developing hemorrhagic complications as might be seen with disseminated intravascular coagulopathy (DIC) (4, 5).

Prothrombotic manifestations of COVID-19

Subsequently, multiple reports have appeared documenting an increased incidence of venous thromboembolism (VTE) in COVID-19 positive patients, particularly those who required care in an ICU setting (6, 7). The cumulative frequency of symptomatic VTE was 25% by 21 days in one study (7), and these events occurred in some patients despite the use of VTE prophylaxis. Using surveillance ultrasound imaging, a second study reported a frequency approaching 70% of patients with severe COVID-19, but almost a quarter of these patients had superficial venous thrombosis (8). In contrast, other studies have found a lower frequency of radiographically-confirmed VTE (7.6% in critically ill patients) and bleeding rates that were not insignificant (5.6% in critically ill patients) (5). Arterial events, including ischemic stroke, MI, and peripheral arterial thromboembolism have also been reported, although they appear to occur less frequently than VTE (9, 10).

Several studies have suggested that for hospitalized patients with COVID-19, prophylactic dose anticoagulant therapy may be insufficient (6, 7). In addition, a recent retrospective cohort study reported that systemic therapeutic anticoagulation was associated with improved survival, although this study did not specifically look at patients with thromboembolic events (11). A separate, prospective randomized trial that is part of the NIH-supported ACTIV-4 program will investigate the dose of anticoagulant therapy in the inpatient population.

There are also an increasing number of reports describing patients with COVID-19 who develop thromboembolic events in the outpatient setting. Two recent studies described patients with COVID-19 being evaluated for progressive respiratory symptoms in the Emergency Department, finding PE by CT angiography in 18% to 23% of patients (12, 13). Previously undiagnosed DVT and PE have also been identified by autopsy in patients dying at home or in a nursing home (14), and a case report described an asymptomatic individual with COVID-19 who presented with sudden death due

to massive PE (15). Whether VTE rates are increased in non-hospitalized patients with COVID-19 is unknown, however.

Similarly, limited data exist concerning the risk of thromboembolic complications for patients with COVID-19 in the post-discharge/convalescence setting. One study noted that out of 1,368 patients discharged following a hospitalization related to COVID-19, 61 patients (4.4%) were re-admitted, 10 for a thrombotic event in venous or arterial territory (16).

Extended thromboprophylaxis following hospitalization in non-COVID-19 patients
Multiple studies have documented that a recent hospitalization is associated with an increased risk for VTE in the post-discharge setting. This increased risk for PE and DVT remains markedly elevated for at least the first month after hospital discharge (17). Although several trials have investigated whether an extended course of thromboprophylaxis with an anticoagulant can decrease this increased risk for VTE, none have shown a substantial improvement in the VTE rate (Table 1). There are unique aspects to each of the studies that may have contributed to the observed outcomes, however.

Table 1. Clinical trials investigating thromboprophylaxis in patients hospitalized for acute medical illness.*

Clinical Trial	Arms	Efficacy outcome(s)	Event rate for anticoagulant	Event rate for placebo	Comparisons† (95% CI)
EXCLAIM (18)	(1) Enoxaparin vs. (2) Placebo	Symptomatic VTE at 28 d	0.2%	1.0%	-0.75 (-1.19 to -0.32)
ADOPT (19)	(1) Apixaban (extended course) vs. (2) Enoxaparin (short course)	Total VTE‡ or VTE-related death	2.71%	3.06%	0.87 (0.62-1.23)
MAGELLAN (20)	(1) Rivaroxaban vs. (2) Placebo	Symptomatic non-fatal VTE at 35 d -or- CV death, MI, or ischemic CVA at 35 d	0.6% 1.8%	0.7% 1.6%	0.82 (0.47-1.43) 1.11 (0.79-1.55)
APEX (21)	(1) Betrixaban vs. (2) Placebo	Symptomatic VTE by 42 d	0.9%	1.5%	0.64 (0.42-0.98)
MARINER (22)	(1) Rivaroxaban vs. (2) Placebo	VTE + VTE-related death -or- VTE, MI, CVA, or CV death	0.83% 1.56%	1.10% 2.00%	0.76 (0.52-1.09 0.78 (0.60-1.02)

* Efficacy outcomes reported in this table could be either primary or secondary outcomes, chosen to most closely reflect the study design developed in this protocol. Both MAGELLAN and APEX included an initial anticoagulant for 10 ± 4 days received by all patients, followed by anticoagulant vs. placebo for an additional ~25 days. ADOPT compared apixaban 2.5 mg twice daily for 30 days to enoxaparin 40 mg once daily for 6-14 days.
† EXCLAIM, absolute risk differences; ADOPT, MAGELLAN and APEX, relative risk; MARINER, hazard ratio.
‡ Total VTE includes symptomatic VTE and asymptomatic VTE, determined by screening ultrasounds of study participants.

EXCLAIM studied acutely ill medical patients ≥40 years of age with recently reduced mobility, treated with enoxaparin for 10 days followed by an additional 28 days of enoxaparin or placebo (18). The protocol was modified after interim analyses suggested lower than expected VTE rates to enroll only individuals at higher risk (age >75 yrs; history of VTE; active or previous cancer). The trial showed a decrease in the incidence of VTE, but primarily restricted to women, patients >75

years of age, and with level 1 immobility (18). MAGELLAN also treated patients with an initial 10 days of enoxaparin, and then randomized to rivaroxaban or placebo for an additional 25 days of therapy (20). Rivaroxaban reduced the risk of the primary outcome, symptomatic DVT/PE and asymptomatic DVT, but not of symptomatic VTE alone (20). APEX included a similar design with an initial 10 days of anticoagulant, followed by betrixaban or placebo for an additional 25–32 days (21). There was no significant difference between betrixaban and placebo for the primary outcome, symptomatic and asymptomatic DVT, although there was a decrease in symptomatic VTE (Table 1). MARINER compared 45 days of rivaroxaban to placebo in medically ill patients at an increased risk for VTE on the basis of a modified IMPROVE score of ≥4 (22). The decrease in symptomatic VTE and VTE-related death was not significant (Table 1)

Recent guidelines recommend against the routine use of extended thromboprophylaxis in medical patients following hospital discharge (23), although it is recognized that selected high-risk patients may warrant this approach. The COVID-19 post-discharge patient population, however, potentially represents such a novel high-risk group that might benefit from extended thromboprophylaxis. In particular, the noted increased risk that these patients exhibit for thromboembolic events while hospitalized (5-7), the autopsy data indicating a significant amount of thrombus affecting smaller vessels (14, 24), and the observations that this hospitalized patient population exhibits additional risk factors for VTE (e.g., older age, obesity) all support a study on post-discharge thromboprophylaxis in this patient population.

1.1.1 Thromboprophylactic therapy: rationale and potential risks

For Stage 1 of this adaptive-design trial, we will investigate whether thromboprophylaxis with prophylactic-dose anticoagulant therapy (apixaban 2.5 mg twice daily) can significantly decrease the risk for thromboembolic complications in patients with COVID-19 who are discharged from the hospital compared to matching placebo. Details of this study are provided in Appendix 3. In Stage 1, concomitant aspirin therapy (or other single-agent antiplatelet therapy) is not a contraindication for participation, and participants will be stratified based on whether they need to be treated with a single antiplatelet agent and WHO severity score (<5 vs. >= 5). The primary outcome will be a composite endpoint of venous thromboembolism, stroke, myocardial infarction, peripheral arterial thromboembolism, and all-cause death.

Potential risks associated with participation in this trial include bleeding complications, and patients with a clinical contraindication to anticoagulant therapy (e.g., gastroduodenal ulcer, major surgery within 14 days, ischemic stroke, intracranial bleed or surgery within 3 months, known hemorrhagic diathesis) or thrombocytopenia (platelet count <50,000/mcL) would be excluded from participation in the randomized study. Bleeding rates associated with the trials presented in Table 1 are shown in Table 2 below.

Table 2. Bleeding rates in clinical trials investigating thromboprophylaxis in patients hospitalized for acute medical illness.*

Clinical Trial	Arms	Safety outcome(s)	Event rate for anticoagulant	Event rate for placebo	Comparisons† (95% CI)
EXCLAIM (18)	(1) Enoxaparin vs. (2) Placebo	Major bleeding	0.8%	0.3%	0.51 (0.12-0.89)
ADOPT (19)	(1) Apixaban (extended course) vs. (2) Enoxaparin (short course)	Major bleeding	0.47%	0.19%	2.58 (1.02-7.24)
MAGELLAN (20)	(1) Rivaroxaban vs. (2) Placebo	Major bleeding at 35 d -or- Clinically relevant bleeding at 35 d	1.1% 4.1%	0.4% 1.7%	2.9 (1.60-5.15) 2.5 (1.85-3.25)
APEX (21)	(1) Betrixaban vs. (2) Placebo	Major bleeding -or- Major or clinically relevant non-major bleeding	0.7% 3.1%	0.6% 1.6%	1.19 (0.67-2.12) 1.97 (1.44-2.68)
MARINER (22)	(1) Rivaroxaban vs. (2) Placebo	Major bleeding -or- Nonmajor clinically relevant bleeding	0.28% 1.42%	0.15% 0.85%	1.88 (0.84-4.23) 1.66 (1.17-2.35)

* MAGELLAN and APEX included an initial anticoagulant for 10 ± 4 days received by all patients, followed by anticoagulant vs. placebo for an additional ~25 days. ADOPT compared apixaban 2.5 mg twice daily for 30 days to enoxaparin 40 mg once daily for 6-14 days.

† EXCLAIM, absolute risk differences; ADOPT, MAGELLAN and APEX, relative risk; MARINER, hazard ratio.

2. Study Design

2.1 Overall Study Design

This trial is an adaptive design protocol intended to determine the optimal antithrombotic strategy to prevent thromboembolic complications in patients hospitalized with COVID19 following discharge from the hospital. The first Stage is a randomized, double-blind, placebo-controlled study comparing a prophylactic dose anticoagulant (apixaban 2.5 mg twice daily; venous thromboembolism prophylaxis dose) with matching placebo (Figure 1).

Subsequent Stages of this adaptive protocol will incorporate new data as it becomes available in this rapidly evolving clinical and research environment. Each Stage will be developed as a separate, detailed Appendix to the Master Protocol. Each Stage will use concurrent control arm data, and no data (from either treatment arm) collected in earlier Stages will be used in subsequent Stages. A full Statistical Analysis Plan will be developed for each Stage, and each new Stage will be submitted with the Statistical Analysis Plan for review by the FDA before implementation.

2.2 Randomization

Randomization will be performed for study participants as close to the time of hospital discharge as possible. Hospitalized patients may be screened and approached about the study up to 72 hours prior to hospital discharge, but final enrollment and randomization should occur as close to the time

of discharge as possible. In Stage 1, participants will be randomized in a 1:1 ratio using an online randomization system to either Arm A (apixaban 2.5 mg twice daily); or Arm B (matching placebo). The randomization scheme will be determined by the study phase and its associated group of intervention arms. Randomization for Stage 1 will be stratified by (1) concomitant use of a single antiplatelet agent (yes/no), and (2) a maximal score of 5 or greater vs. a score of less than 5 by the WHO Ordinal Index (Table 3).

Table 3. **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

*chronic CPAP or BiPAP use for sleep apnea excluded

2.3 Study Interventions

This master protocol study will open by comparing a prophylactic anticoagulant therapy in Arm A, and matching placebo in Arm B, as described in Appendix 3.

2.4 Biorepository

A biorepository will be established to biobank samples for further studies of biomarkers of thrombotic risk and inflammation. Centers capable of collecting, processing, and shipping samples may opt in for collecting and biobanking these samples from eligible participants. As an alternative to collecting samples by phlebotomy, sites/participants may be able to send biobank samples through dry blood spots for both Day 0 and Day 30. There will be a nested design to the biobanking strategy, so that sites can participate based on level of expertise, staffing, and interest. The initial samples proposed for the biorepository are listed in Appendix 4.
Biorepository specimens may change during different stages of this adaptive design protocol.

3. Objectives and Purpose

The overarching objective of this adaptive research trial design is to iteratively learn which antithrombotic strategy is best for the prevention of thromboembolic complications in patients with COVID-19 who have been hospitalized for two or more days and are being discharged from the hospital, during the post-discharge/convalescence phase of the illness. At each Stage of the trial, the goal is to determine the superior approach that should be considered standard care for this patient population. Subsequent stages will introduce alternative strategies and/or designs that will be compared to this new standard of care in an iterative fashion. This process will continue until there are no new strategies that replace the standard of care.

The primary outcome for Stage 1 will be a composite endpoint of venous thromboembolic events, including new, symptomatic proximal or distal deep vein thrombosis affecting the upper and/or lower extremities, pulmonary embolism, or thrombosis of other veins (e.g., cerebral sinus veins, splanchnic veins); arterial thromboembolic events, including new ischemic stroke, myocardial infarction, mesenteric or peripheral arterial thromboembolism; and all-cause mortality for up to 30 days after randomization. This primary outcome is expected to be similar across all stages of this study, although it is possible that changes could be introduced on the basis of results accrued during the study.

Primary Objective: In COVID-19 patients who have been hospitalized, the primary objective of this master trial is to determine the optimal antithrombotic strategy to minimize the composite endpoint of venous and arterial thromboembolic outcomes, and all-cause mortality. Stage 1 of this trial will compare the effects of treatment beginning at the time of discharge from the hospital with either (i) anticoagulation at a prophylactic dose, or (ii) no anticoagulation on the primary outcome for up to 30 days after randomization. See Appendix 3 for details of Stage 1. Randomization is expected to occur on the day of discharge.

Secondary Objectives:

Secondary Objective 1: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of the composite outcome at 45 days and at 90 days after randomization.

Secondary Objective 2: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of new, symptomatic VTE (inclusive of DVT, PE, or other venous thrombosis) for up to 30 days after randomization.

Secondary Objective 3: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of new, symptomatic ATE (inclusive of ischemic stroke, MI, or peripheral arterial thromboembolism) for up to 30 days after randomization.

Exploratory Objectives:

Exploratory Objective 1: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of all-cause rehospitalization for up to 90 days after randomization.

Exploratory Objective 2: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of all-cause mortality for up to 30 days after randomization.

4. Study Design and Endpoints

Stage 1 of the protocol is described in Appendix 3. Subsequent stages will incorporate recommendations from the DSMB based on the accrued in-trial data at prespecified timepoints or at selected milestones of participants accrued into the study. Adaptive changes may impact the treatment arms (e.g., modifications to the antithrombotic agent or regimen, duration of therapy), patient eligibility (e.g., identification of unique patient characteristics associated with a higher or

lower risk of the primary outcome), endpoints (e.g., addition of alternative endpoints), or any combination of these variables.

4.1 Description of Study Design: Stage 1

The Stage 1 study is a randomized trial of COVID-19 positive patients who have been hospitalized and are ready for discharge from the hospital. All inclusion and exclusion criteria (Sections 5.1 and 5.2, below) must be met prior to enrollment and randomization. In Stage 1, participants will be randomized to either Arm A (apixaban 2.5 mg twice daily), or Arm B (matching placebo) (Figure 1). Potential study participants will be identified through review of inpatient census data at each site.

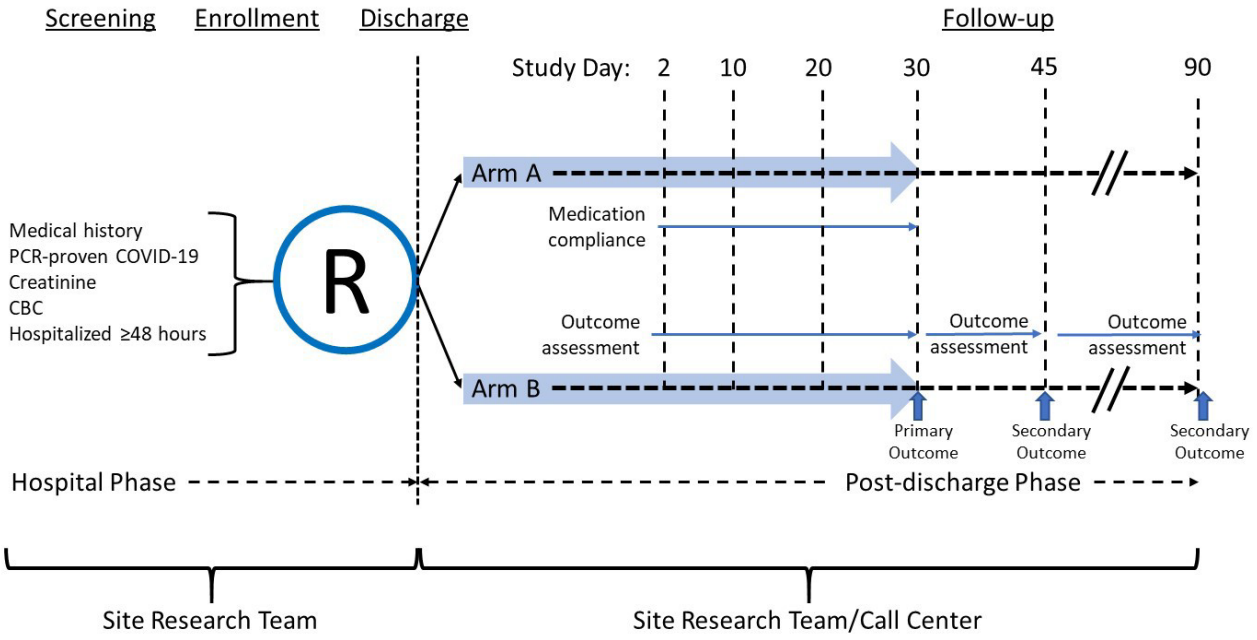

Figure 1. COVID-19 Post-Discharge Clinical Trial Stage 1. Participants will be enrolled in the Study prior to discharge from the hospital and randomized to one of two Arms (this general design may change with adaptations during the course of the study). Screening and enrollment will occur prior to discharge from the hospital, with randomization occurring as close to discharge as possible (randomization identified as the encircled "R", occurring immediately prior to discharge, identified by the vertical dashed line). Follow-up encounters for the primary outcome will occur on Days 2, 10, 20, and 30. Two additional follow-up encounters will occur for secondary outcomes on Days 45 and 90. The Day 45 follow-up encounter will also be included to ensure the 2nd biorepository specimens have been collected for those participating in this part of the study.

The initial follow-up encounter, which will be conducted by the Call Center via the participant's preferred method (electronic or phone call), will occur within 2 days following discharge from the hospital, to confirm study medication adherence and perform an initial assessment of outcomes. Subsequent encounters, which will also be conducted by the Call Center electronically or by phone, will occur at 10, 20, and 30 days after enrollment. With each encounter, assessments of medication adherence and outcomes will be performed. Two additional encounters will occur after completion of the primary outcome, at 45 and 90 days after enrollment, to determine if there is an increased risk for thromboembolic complications following hospital discharge that extends for a longer period of time than 30 days and to facilitate/confirm collection of the 2nd set of biorepository specimens. All contacts will be scripted to ensure that all information is uniformly collected.

4.2 Study Endpoints for Stage I

4.2.1 Primary Study Endpoints

At approximately day 30 from randomization, a binary composite endpoint of venous and arterial thrombotic complications—including new, symptomatic proximal, or distal DVT of the upper or lower extremities, PE, and new thrombosis of other veins (including cerebral sinus and splanchnic veins), ischemic stroke, myocardial infarction, other arterial thromboembolism (e.g., mesenteric or acute limb ischemia), and all-cause mortality will be the primary study endpoint.

4.2.2 Key Secondary and Exploratory Endpoints

Key secondary endpoints include the following.

1. The composite endpoint for the primary outcome at day 45 following randomization
2. The composite endpoint for the primary outcome at day 90 following randomization
3. Composite endpoint of venous thromboembolic events, including symptomatic DVT of the upper or lower extremities, symptomatic and/or clinically relevant PE, and other symptomatic venous thrombosis, including cerebral sinus and splanchnic vein thrombosis at day 30
4. Composite endpoint of arterial thromboembolic events, including symptomatic ischemic stroke, myocardial infarction, and other symptomatic arterial thromboembolic events at day 30

Secondary endpoints will be formally tested using a fallback approach only if the primary endpoint was statistically significant at the two-sided 5% level.

Exploratory endpoints include the following.

1. All-cause mortality at day 30 following discharge from the hospital
2. All-cause re-hospitalization at day 90 following discharge from the hospital

4.2.3 Safety Endpoints for Stage 1

Safety endpoints will include (1) major bleeding, as defined by the ISTH, and (2) clinically-relevant, non-major bleeding, also as defined by the ISTH. Criteria for major bleeding, and for CRNMB are provided below

1. Major bleeding
    a. Fatal bleeding
    b. Bleeding into a critical area or organ (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)
    c. Bleeding causing a fall in the hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells
2. Clinically-relevant, non-major bleeding
    a. Bleeding requiring medical intervention by a healthcare professional
    b. Bleeding leading to hospitalization or an increase in the level of care
    c. Bleeding prompting a face-to-face (i.e., not just a telephone or electronic communication) evaluation

4.2.4 Adjudication of outcome events

All patient-reported events will be investigated by the Clinical Coordinating Center, including obtaining information from healthcare facilities where the patient received treatment. An

independent, central adjudication committee (ICAC) will review and adjudicate events in a blinded manner without knowledge of treatment allocation. During the study period, the ICAC will adjudicate all suspected occurrences of venous or arterial thromboembolic events, ischemic stroke, acute myocardial infarction, deaths, and re-hospitalization. The ICAC will also review all suspected episodes of bleeding that require medical attention and categorize adjudicated bleeding as major, clinically-relevant non-major, or minor bleeding. The Committee will be provided with all relevant documentation related to the events. The criteria and definitions of the study outcomes, as well as the procedures followed by the Committee, will be described in an adjudication manual which will be provided to the ICAC members prior to the first meeting.

5. Study Enrollment

5.1 Inclusion Criteria

The inclusion criteria for Stage 1 of this adaptive protocol are listed below and in Appendix 3. Potential study participants will be identified during hospitalization and reviewed for inclusion/exclusion criteria. Per the adaptive trial design strategy, these criteria may change after the first and subsequent analyses of in-trial accrued data.

- Age ≥ 18 years
- COVID-19 positive test (PCR, antigen, or point of care test diagnosing a current infection) within 2 weeks of hospital admit date
- Hospitalized for COVID-19 infection for 48 or more hours

5.2 Exclusion Criteria

The exclusion criteria for Stage 1 of this adaptive protocol are listed below and, with additional details, in Appendix 3. These are potentially subject to change based on the adaptive trial design and analyses of in-trial accrued data.

- Existing indication for anticoagulation, either therapeutic or prophylactic dose
- Contraindication to antithrombotic therapy, such as
    - Ischemic stroke, intracranial bleed, or neurosurgery within 3 months
    - Known bleeding within the last 30 days requiring emergency room presentation or hospitalization
    - Known major surgery within 14 days (at least 1 hour and/or requires general anesthesia)
    - Inherited or active acquired bleeding disorder
- Platelet count < 50,000/mcL
- Hemoglobin < 8 gm/dL
- Pregnancy
- Prison inmate
- Life expectancy less than 90 days
- Unwilling or unable to provide informed consent / unwilling or unable to complete the study protocol
- Other criteria related to stage-specific appendices developed as adaptations to the trial. (i.e. Stage 1 is in appendix 3)

5.3 Vulnerable Subjects

As noted in the Exclusion Criteria, this study will not enroll children < 18 years of age, pregnant women, or prisoners.

5.4 Strategies for Recruitment and Retention

The Protocol Implementation Committee (PIC) will respond to the evolving landscape of the pandemic by leveraging the network of networks already established within ACTIV-4, including all sites participating within the networks. As is currently evident, the pace of the pandemic varies across different areas within the United States, based on propagation patterns, local social distancing rules, and compliance with those rules. In addition, the PIC will also be monitoring the course of the pandemic across the world to identify regions where the number of potential study subjects would make rapid recruitment feasible. By monitoring the evolution of the infection, the PIC will place sites on hold when disease activity wanes in their geographic areas and activate new sites when the local rate of new COVID-19 cases exceeds a threshold making recruitment feasible.

Screening and enrollment will occur within the hospital setting, targeting patients being considered for discharge within 72 hours. Providers managing these patients will be made aware of the study, and the research team at each site will review the list of inpatients to identify potentially eligible patients for the study. Study participants will be provided with study drug at the time of discharge from the hospital, with detailed instructions for taking the medication. At those sites with the capability to process and store biospecimens, those patients who agree to participate will be asked to provide samples for preparation of plasma, serum, and genomic DNA, as described below.

The local study team will collect relevant contact information for the participant, participant's spouse or partner, one contact individual who is not related to the participant to maintain contact, and the participant's Primary Care Physician. The local study team will inform the participant about the Call Center's role and, if possible, put the phone number in the participant's phone so they recognize the caller later. The participant will be asked to sign a Release of Records form for the PCP or other hospital. This form will have an expiration date 150 days after randomization.

One encounter with the study participant will occur at one to three days after discharge, to confirm medication compliance and collect information concerning any early outcome events. Five additional encounters for confirming compliance with the protocol and collecting outcome information will occur at 10 days, 20 days, 30 days, 45 days, and 90 days from initiation of the study. These visits may be set up to be electronic only (e-mail or text) or by telephone, depending on which approach works best for the individual study participant. The study is completed within approximately 90 days of hospital discharge.

Site investigators will be educated about the importance of retention of subjects in the study and will be informed about the steps that will be taken to prevent missing data. Study participants will be educated about the importance of their completion of the study and the different options available for them to accomplish this objective. Study participants who discontinue treatment with the study medication will continue to be followed by the study team unless the participant requests to be withdrawn from the study. Regular web-based and/or phone-based contacts during the course of study participation are designed to maintain ongoing interaction and support retention in the study.

Enrollment and retention of economically-disadvantaged individuals. The overall success of this study is critically dependent on the ability of all patients who meet inclusion/exclusion criteria to participate in the study. Populations historically affected by health disparities, including non-Hispanic Blacks and Hispanics, have been shown in several studies to be disproportionally affected by and hospitalized with COVID-19 (25, 26). These populations are also disproportionally affected by economic disparities, which can lead to difficulties with obtaining costly outpatient medications, leading to non-compliance. Consequently, the first stage of this study will provide the anticoagulant and the matching placebo to eliminate this potential reason for not participating in the study. This

approach will ensure that this study is relevant to the entire range of patients hospitalized with COVID-19.

5.5 Duration of Study Participation

Study participation lasts from the time the participant is enrolled into the study until 90 days from hospital discharge.

Total Number of Participants

Sample size calculations for Stage 1 are described in Section 7. Initial power calculations using conservative event rates from post-hospital extended duration VTE prophylaxis trials in medically ill patients selected for increased risk suggest that 2,660 participants per arm will be required to determine if thromboprophylaxis with an anticoagulant is superior to no anticoagulant thromboprophylaxis. There will be interim monitoring to enable early stopping for futility, efficacy, or safety.

5.6 Participant Withdrawal or Termination

5.6.1 Reasons for Withdrawal or Termination

Study participants are free to withdraw from participation in the study at any time upon written request. The site PI will notify the Clinical Coordinating Center of all withdrawals from the study. Study participants who withdraw consent will not have additional information collected after they withdraw from the study.

A site investigator may discontinue study drug for a study participant on the basis of either:

- Any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued study drug treatment would not be in the best interest of the patient.
- The participant meets an exclusion criterion, either newly developed or not previously recognized (e.g., new thrombocytopenia, renal insufficiency), that precludes further study medication continuation.

Study participants may choose to withdraw from participation in the study at any time.

As noted above, study participants who discontinue taking the study drug prior to completing 30 days of therapy will continue to be followed as study participants, unless they also request to be withdrawn from the study.

5.6.2 Premature Termination or Suspension of Study

All deaths, SAEs, and related clinical events within the study period will be reviewed by the DSMB. The decision to stop or suspend the study will be made by the DSMB after considering the totality of the data and the benefit-risk of continuing the study. These decisions could lead to an adaptive change in the protocol, with one arm of the study being discontinued or modified/changed to an alternative approach.

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

5.7 Study Agents

Study agents for Stage 1 (described in more detail in Appendix 3) include:

1) Prophylactic anticoagulant, defined as a dose intended for the prevention of VTE; and
2) Matching placebo

Subsequent adaptations of this study may focus on modifications to the antithrombotic strategy, specific subsets of patients identified as being higher-risk for thrombotic complications, or other changes, as outlined in Figure 1.

5.8 Duration of Therapy

Duration of the thromboprophylaxis period will be 30 days, beginning at the time of discharge from the hospital. Primary outcome will be assessed by approximately 30 days after randomization. Study participants will be followed for an additional 60 days after discontinuation of thromboprophylaxis (total duration of study participation = approximately 90 days).

Study agents for subsequent stages will be determined based on the adaptive design of the trial.

6. Study Procedures and Schedule

6.1 Study Schedule

Activity	Baseline screening	Enrollment (~Days -3 to 0)	Randomization (Day 0)	Day 2	Day 10	Day 20	Day 30	Day 45	Day 90
Eligibility Assessment									
Medical history	X								
SARS-Cov 2 test positive	X								
Creatinine/eGFR	X								
CBC	X								
Enrollment & Randomization									
Informed consent		X							
Baseline data collection		X							
D-dimer		X							
Pregnancy testing (if necessary)		X							
Randomization			X						
Study Drug Administration									
Study drug provided			X						
Patient education			X	X	X	X	X		
Confirmation of study drug taken				X	X	X	X		
Study Procedures									
Confirm study drug adherence				X	X	X	X		
Outcome assessment				X	X	X	X	X	X
AE assessment and reporting		X	X	X	X	X	X	X	X
Laboratory Assessments									

Biorepository samples (substudy, optional)			X					X*	

Second biorespository sample should be collected between Days 30 and 45, after the patient has discontinued study drug.

6.2 Laboratory Procedures/Evaluations

All study participants will have either (1) clinical/standard of care D-dimer results or (2) a study D-dimer drawn within 72 hours prior to randomization. Hgb, Creatinine, and Platelet Count can be within 72 hours prior to study enrollment. The creatinine is used in the calculation of the eGFR, and a eGFR <30 mL/min/1.73 m2 is an exclusion criterion (see Stage 1 exclusion criteria in Appendix 3). Include the LFT, LDH and Albumin if completed during the participant's hospital stay. These results (LFT, LDH, and Albumin) can be the most recent if not drawn within 72-hour of hospital discharge.

In addition, participants who consent to the biorepository substudy will be given the option of providing a blood sample by phlebotomy or independently mailing in a dry blood spot sample at two time points:

1) On Day 0, prior to initiation of the study drug
2) Between Days 30 and 45, after the patient has discontinued the study drug.

The proposed samples to be collected for the biorepository during Stage 1 of the study are reviewed in Appendix 4. Samples collected for the biorepository may change to accommodate the adaptive design of the study in response to changes in trial design.

6.2.1 Study encounters

Baseline screening and enrollment (occurs ~Day –3 up to Day 0)

1. Inclusion/exclusion criteria reviewed—including a pregnancy test, if necessary—and eligibility for the trial determined. Prior urine or serum pregnancy test results accepted as long as they are obtained within the hospitalization. Abstinence does not count as a reason not to obtain a pregnancy test.
2. Patient enrolled into the study and informed consent obtained
3. Patient provided with information concerning the study, contact information, etc.
4. Occurs during last few days of hospitalization

Encounter 1: Randomization (Day 0)

1. Patient randomized to study drug
2. Information concerning the study, contact information, etc., reviewed with the patient
3. Clinical/standard of care D-dimer results or a study D-dimer drawn within 72 hours prior to randomization
4. Randomization expected to occur on day of discharge from the hospital

Encounter 2: First follow-up (Day 2)

1. First post-discharge encounter
2. Confirm taking study medication, review for any outcome events, adverse events

Encounter 3: Day 10

1. Second post-discharge encounter
2. Confirm taking study medication, review for any outcome events, adverse events

Encounter 4: Day 20

1. Third post-discharge encounter
2. Confirm taking study medication, review for any outcome events, adverse events

Encounter 5: Day 30

1. Fourth post-discharge encounter
2. Confirm taking study medication, review for any outcome events, adverse events
3. Participant will stop taking the study medication on Day 30
4. Events occurring up to this encounter will be included in the primary outcome
5. Make and confirm arrangements for second biorepository encounter

Encounter 6: Day 45

1. Fifth post-discharge encounter
2. Review for any outcome events, adverse events
3. Confirm second biorepository encounter has occurred

Encounter 7: Day 90 encounter

1. Sixth and last post-discharge check-in
2. Review for any outcome events, adverse events
3. Follow-up ends after the Day 90 encounter

6.3 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:

1. Antiplatelet therapies (e.g., aspirin, clopidogrel)
2. Anticoagulant medications that may be prescribed to the participant after randomization and discharge from the hospital (e.g., a new prescription introduced by an outpatient provider, without notification of the study team, in response to a clinical concern about thrombosis risk or symptoms)
3. Other therapies that may impact arm-specific appendices

6.4 Expedited Critical and Major Event Reporting

All efficacy and safety outcome events will be assessed and documented in the patients' study records. Events meeting the DSMB-specified *severe* criteria will be reported within 1 business day of Safety being notified. These events include major bleeding (fatal bleeding or symptomatic bleeding in a critical area or organ), including intracranial hemorrhage.

The ACTIV-4c trial will have a common 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. Sites are required to follow their local guidelines for adverse event and unanticipated problem reporting.

6.5 Data and Safety Monitoring Plan and Study Halting Rules

The ACTIV-4 will have a single Data and Safety Monitoring Plan with a single Data and Safety Monitoring Committee to review all research carried out within the master protocol.

7. Statistical Considerations

7.1 Statistical and Analytical Plans (SAP)

This section provides an overview of the design and main analyses for the key endpoints. A separate SAP will be constructed for the DSMB review process. Additionally, a final SAP will be formalized and agreed upon by the study team prior to the completion of the study and before database lock for each stage. The final SAP will include additional details about the statistical analyses, including analysis of specified populations, plans for addressing missing data, and planned sensitivity analyses.

7.2 Power and Sample Size Calculations

The primary analysis for this randomized trial will be an intention-to-treat comparison of a composite endpoint (CE) of venous thromboembolic events, including new, symptomatic proximal or distal deep vein thrombosis affecting the upper and/or lower extremities, pulmonary embolism, or thrombosis of other veins (e.g., cerebral sinus veins, splanchnic veins); arterial thromboembolic events, including new ischemic stroke, myocardial infarction, mesenteric or peripheral arterial thromboembolism; and all-cause mortality for up to 30 days after randomization across the intervention arms. This binary primary endpoint was used to power the study.

The MARINER trial (21) reported a 2% event rate for a combined outcome of VTE, MI, CVA, or CV deaths in the placebo group. These rates are expected to be higher in COVID-19 patients who are discharged from the hospital. Recent information from patients discharged alive from the University of Pittsburgh Medical Center suggests that the 30-day mortality rate in this population could be as high as 4%. To be conservative, 4% was used as the expected CE rate of events for the no anticoagulant arm. An effect size of 35% percent risk reduction (risk ratio = 0.65) in the anticoagulant group compared to no anticoagulant group was used to calculate the expected sample size for the study.

The analysis will use a group-sequential two-sample two-sided Z-test for proportions with pooled standard deviation to test the primary hypothesis at overall significance level alpha = 0.05. Four equally spaced interim analyses and one final analysis will use O'Brien-Fleming alpha spending boundaries for decision-making (27, 28). In order to ensure an 80% power to detect a CE rate reduction of 35% through anticoagulation use, the study needs to enroll at least 2,530 participants per arm. Since the primary outcome is observed within 30 days of follow-up, the loss to follow-up and withdrawal of consent rates should be low, and it is estimated that CE will be missing on a maximum of 5% of the participants. Therefore, the sample size required for this study will be approximately 2,660 per arm. The sample size has been calculated using 2,000 simulations in PASS 13 [PASS 13 Power Analysis and Sample Size Software (2014). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass].

7.3 Primary Outcome Analysis

The ITT principle will be used for the treatment comparisons of trial outcomes such that subjects randomized to the treatment arms will be included in the analysis. Trial follow up will begin at the time of randomization. In other words, Day 0 is the day of randomization.

As a primary approach, the primary endpoint will be compared between two arms using a two-sample Z-statistic for proportion (standardized difference between proportion having CE in anticoagulant arm and matching placebo arm, positive difference favoring anticoagulant arm). More explicitly, denoting pp, pp_{AA} and pp_{PP} the estimated proportion of CE in the whole sample, anticoagulant and placebo group respectively, the null hypothesis of no difference in the proportions will be tested using the test statistic

$$Z = (p_P - p_A)/SE(p_P - p_A),$$

where $SE(p_P - p_A)$ will be estimated by pulling over the two groups, that is

$$SE(p_P - p_A) = \sqrt{\left[p(1-p)\left(\frac{1}{n_P} + \frac{1}{n_A}\right)\right]},$$

where n_P and n_A are the sample sizes for the placebo and anticoagulant groups, respectively.

For Stage 1, the CE rates will also be modeled using a log-binomial regression model with treatment arm as the independent variable and adjusting for trial stratification variables (i.e., antiplatelet use; WHO ordinal scale score). Secondary analyses of this endpoint will include

adjustment for D-dimer levels, patient characteristics, and demographic factors, including race and ethnicity. The matching placebo arm will serve as the “reference group” in this model, and analysis will involve testing whether the coefficient for each active treatment group relative to the reference group is equal to 0, or equivalently, whether the adjusted relative risk for anti-coagulant arm is equal to 1. The adjusted relative risk and the related confidence interval will be provided.

In addition, unadjusted event rates for each treatment group, and relative risk and the absolute risk differences with confidence intervals, will be calculated and presented. Kaplan-Meier cumulative incidence curves will also be presented to allow visualization of the patterns of time to first events. As a sensitivity analysis, a modified intention-to-treat analysis, excluding all randomized participants who fail to initiate treatment, will be conducted.

7.4 Secondary and Exploratory Endpoints Analyses

There are four secondary outcomes that are of interest in this trial. We will use a fallback method to control for type I error (see page 30 of the Food and Drug Administration guidance on multiple endpoints in clinical trials; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry). More specifically, these secondary outcomes will only be formally tested if the primary hypothesis was rejected at level alpha=0.05. The ordering of the secondary endpoints is as follows:

1) Primary endpoint at 45 days (CE45)
2) Primary endpoint at 90 days (CE90)
3) Venous events at 30 days (CEVTE30)
4) Arterial events at 30 days (CEATE30)

Using a fallback method the 0.05 type I error rate would be split as follows – 0.035, 0.005, 0.005, and 0.005. If CE45 was statistically significant then CE90 would be tested at 0.04 = 0.035 + 0.005. On the other hand, if CE45 was NOT statistically significant then CE90 would be tested at 0.005. The process would continue until all 4 secondary endpoints were tested.

Statistical methods for testing the secondary endpoints listed above will follow exactly the same procedures used for the primary endpoint described in Section 4.2 above. Except that for the CEVTE30 and CEATE30 events, an additional sensitivity analysis will be conducted by combining death from any causes to each one of the events separately.

7.5 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 all clinical endpoint events that occur during the 30-day treatment period will be collected regardless of whether a patient discontinues therapy or experiences an initial clinical event. As a result, some participants may experience more than one component of the primary endpoint. Event rates and relative risks and the absolute risk difference between treatment groups will be calculated with their confidence intervals for each of the defined secondary endpoints.

7.6 Sub-group Analyses

A select number of subgroup analyses will be performed based on pre-specified baseline factors that potentially modify the effect of treatment. The main subgroup analyses will be done for antiplatelet use and no antiplatelet use groups, and for severity of illness during hospitalization, based on the WHO ordinal scale score (score < 5, vs. ≥ 5). Additional subgroup analysis are described in section 7.6.6. When outcomes are rare within subgroups, the categories may be

amalgamated (e.g., White vs. Others, US vs. Other countries). The rate of the 30-day primary composite outcome and the safety outcomes will be compared by assigned treatment within pre-defined subgroups. In addition, an assessment of whether there is evidence that each subgroup variable modifies treatment effectiveness will be performed by creating a log-binomial regression model including the subgroup variable, treatment assignment, and the interaction between the subgroup variable and treatment assignment, and evaluating the magnitude of the interaction term.

7.6.1 Safety Analyses

The rates of safety outcomes listed in section 2.3 (e.g., ISTH major bleeding and the rate of ISTH clinically relevant non-major bleeding (CRNMB)) during the 30-day treatment period and during the additional 60-day safety follow up period between the two arms will be compared. The proportion of patients in each assigned treatment group who experience each safety event, the relative risk, and the absolute risk difference will be calculated from the observed data, and confidence intervals will be calculated. Analyses of the bleeding outcomes that occur during the full 90-day follow-up period (i.e., 30-day treatment period plus the 60-day safety follow-up) will also be conducted as part of the trial safety analyses

7.6.2 Adherence and Retention Analyses

Receipt of planned therapy will be recorded on electronic case report forms. The proportion of patients evaluated with less than 30-days of follow-up (the primary outcome assessment time) will be tabulated. Every effort will be made to re-contact patients who are unreachable. Due to the short timeline of trial participation, there should be excellent patient retention. A thorough evaluation of missing data patterns will be undertaken. Baseline characteristics of patients with missing primary outcome data will be compared to those with complete data; factors associated with missing primary outcome data will be identified using logistic regression. Missing follow-up data will not be imputed for the analysis of the primary hypothesis unless critical issues are identified.

7.6.3 Baseline Descriptive Statistics

A limited number of demographic, clinical history, symptom, and biomarker variables will be collected for each patient at baseline. The distribution of each variable will be examined. All variables will be summarized using appropriate central tendency (mean/median) and spread measures (standard deviation, 25^{th} and 75^{th} percentiles, or range) for continuous variables and frequency and percent for categorical variables. Baseline characteristics will be examined with respect to assigned treatment group to verify randomization balance.

7.6.4 Planned Interim Analysis, Futility, and Efficacy

An independent data safety and monitoring board (DSMB) will review all interim analyses prepared by an unmasked statistician. The trial design planned for 4 interim analyses and a final analysis at equally-spaced information points. At each interim analysis cumulative primary outcome data, and potentially the secondary analyses, will be presented to the DSMB. Based on the data, a decision to stop or continue the trial will be taken following the O'Brien-Fleming Rule. If the Z-statistic crosses the lower boundary, the trial will be stopped for futility while if the Z-statistic crosses the upper boundary, the trial will be stopped declaring anticoagulant to be effective in preventing CE. In either case, Stage 1 of the trial will end and secondary analyses, including subgroup analyses will be critical for driving adaptive changes made based on accrued data. Eligibility criteria, efficacy, and safety endpoints will be analyzed at predefined intervals to guide the design of subsequent stages to allow efficient use of data and resources to inform the adaptations in trial design.

Assessments of futility will be conducted at all interim looks, whereas efficacy will only be assessed starting at the third interim analysis (after 60% of the information accumulated; Table 4). For the efficacy and futility, O'Brien-Fleming analog alpha-spending function and Hwang-Shih-DeCani beta-spending function will be utilized to create the non-binding boundaries. Table 4 and Figure 2 provide specific efficacy and futility boundaries at each interim analysis..

Table 4: Stopping Boundaries for Efficacy and Futility based on Z-statistic above.

Look	Information proportion	Efficacy Boundary	Futility Boundary
1	20%	NA	0.1383
2	40%	NA	-0.5933
3	60%	-2.6686	-1.1439
4	80%	-2.2887	-1.5918
Final	100%	-2.0307	-2.0307

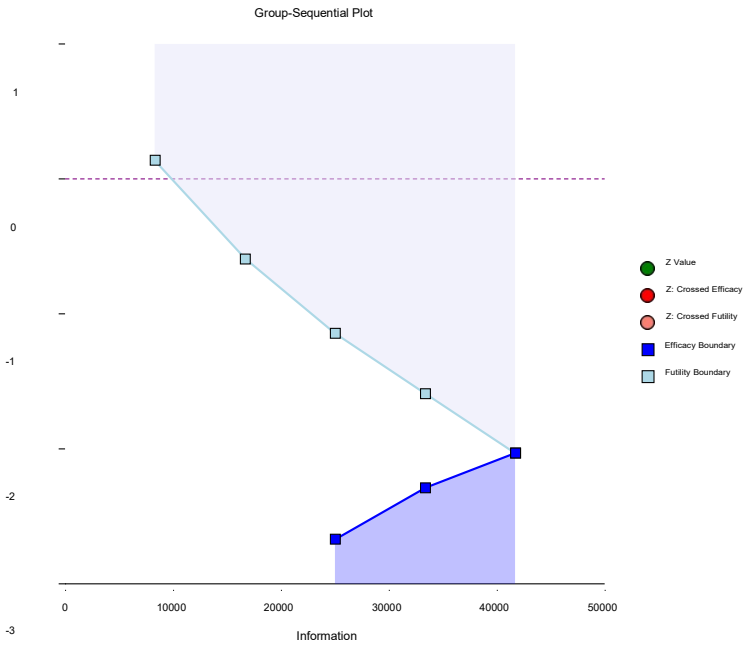

Figure 2: Stopping Boundaries for Efficacy and Futility based on the Z-statistic described above

7.6.5 Safety Review

Safety monitoring will be continuous. In addition to examining the rate of ISTH major bleeding and the rate of ISTH clinically relevant non-major bleeding (CRNMB) in each of the treatment arms, monitoring will include unacceptable toxicity, defined as major bleeding, including hospitalization, and all-cause mortality. Prior studies have shown that the rate of major bleeding will be very low. The degree of evidence about differences in risk of unacceptable toxicity from accruing data will be addressed on a regular and pre-determined basis (e.g. every 3 months) and will be shared with the

DSMB. Unadjusted safety event rates for each assigned treatment group, and relative risks and the absolute risk differences with 95% confidence intervals, will be calculated and presented to the DSMB for each of the specified safety outcomes. Additionally, participants with safety events will be categorized in comparison to those without the safety events using a logistic regression to identify if the safety event was associated with any particular participant characteristics to identify high-risk groups, which will potentially inform DSMB of changing the inclusion criteria.

If safety issues arise, the DSMB will use their clinical and statistical judgement to assess the potential risks relative to the potential benefits. The DSMB may also examine the safety and efficacy data in subgroups known to be high risk for bleeding such as those with older age and/or higher BMI. The DSMB will use all available information to make recommendations to the NHLBI. The DSMB can recommend that the Post-discharge COVID-19 trial should continue as proposed, that one treatment arm or more may be dropped, that the trial protocol should be modified, or that the trial should be terminated early for safety reasons. At any of the safety reviews, the DSMB can request further statistical evaluation of the safety data to make a decision. Only the DSMB and those individuals invited to the DSMB closed-session are permitted to examine outcomes by assigned treatment group. The DSMB will evaluate the rates of the primary endpoint and the safety endpoints by assigned treatment groups overall and within pre-specified subgroups.

7.6.6 Subgroup Analyses based on Anti-Platelet Use, WHO Severity Score, and Other Pre-specified Characteristics

Beyond its primary aim, a major interest of the trial is to address the effect of anticoagulant separately within antiplatelet users and non-users. The primary analysis will be repeated within each of these subgroups. The pre-specified subgroups include

- WHO severity score (below five vs. five or above)
- Antiplatelet use and no antiplatelet use groups
- D-dimer,
- BMI,
- age,
- sex,
- race/ethnicity, and
- country of enrollment.

7.6.7 Analyses of Duration of Treatment

The optimal length of treatment is not well-understood in this clinical setting. Hence, the analyses will examine the timing of clinical thrombotic events and safety hemorrhagic events based on the accruing data. Kaplan-Meier curves will be created to assess the time to the first thrombotic event and the time to the first hemorrhagic event, and Nelson-Aalen cumulative hazard curves will be used to assess the cumulative number of events.

8. Measures to Minimize Bias

8.1 *Enrollment/Randomization*

Enrollment

1. Hospitalized patients confirmed COVID-19 positive are screened daily 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.

Randomization

Randomization assignments are performed for patients at baseline visit. Randomization will be done with equal probability across the arms for which the participant is eligible. For Stage 1, randomization stratification will be done by anti-platelet use (yes/no) and WHO severity score (<5 / >=5).

The randomization scheme will be determined by the study *Stage* and its associated group of intervention arms. Randomization should obviate the need for additional adjustment factors, but if pre-specified demographic or clinical characteristics are unbalanced with respect to treatment group, an adjustment will be considered during the analyses phase; these characteristics include but are not limited to age, sex, race, ethnicity, BMI, and, potentially, country.

9. Source Documents and Access to Source Data/Documents

ACTIV-4 will have uniform policies describing what source documents are, how to make corrections, and who can access them.

10. Quality Assurance and Quality Control

ACTIV-4 will have common policies for quality assurance at the data entry level and site monitoring.

11. Ethics/Protection of Human Subjects

11.1 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.

11.2 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.

11.3 Informed Consent Process

11.3.1 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 a REDCap based e-consent option pending IRB approval of this protocol.

11.3.2 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-19 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.

11.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the study 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.

11.5 Participant and Data Confidentiality

ACTIV-4 has adopted uniform policies for protecting the privacy of participants and maintaining confidentiality.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Participant identifying information will be collected via electronic survey, and will be stored in secure encrypted servers at the University of Pittsburgh. All data will be streamed via secure API to the project clinical trial management system. Identifiers are required in both of these locations to enable electronic outreach to participants for the purpose of self-reported data collection. The participant's name, mobile phone number, address, and contact information will only be housed on a temporary basis to allow for follow-up during the course of the trial. These data will be maintained until database lock at the end of the trial, at which point they will be destroyed, unless the participant has agreed to be contacted for future research.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Pittsburgh Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data in the central database will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NIH designated data repository.

12. Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Initial data collection is the responsibility of the clinical trial staff under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Follow up data will be collected electronically from the participant's self-report and by study staff via telephone. Responsibility for the accuracy, completeness, and timeliness of data collected by telephone is under the supervision of the Coordinating Center investigators who are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the Coordinating Center's official electronic study record.

12.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is

discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 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.

12.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

13. Study Finances

13.1 Funding Source

National Institutes of Health

13.2 Costs to the Participant

There will be no costs incurred related to the study medication, which will be provided by the study, or the baseline D-dimer blood test, if it was not drawn as part of the participants standard of care, which will also be covered by the study. There will also be no costs related to participation in the optional biorepository. 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 was not in the study, if their insurance does not cover these costs or participants do not have insurance, these costs will be participant responsibility.

14. Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies.

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Appendix 1: Criteria for Addition and Replacement of Arms

This master protocol trial design is built as a process, with the possibility of multiple interventions being investigated. In subsequent stages, this trial may incorporate 2 or more interventions, and the number of interventions may evolve as the science evolves and as data accrues during the course of the trial.

Appendix 2: Definition and Determination of Outcomes

A2.1 Approach to ascertainment and verification of outcomes

Patients will be enrolled and randomized in the inpatient setting, prior to discharge from the hospital (see Figure 1 in the main protocol). A total of six follow-up contacts would be made during the course of the study, at study days 2, 10, 20, 30, 45, and 90. Although one or more of these encounters may occur as part of an in-person study visit, we anticipate that most of these encounters will occur via remote telephone monitoring. All patient reported events will be investigated by the Central Coordinating Center, including obtaining information from healthcare facilities where patients received treatment and/or were admitted to the hospital. An independent central adjudication committee (ICAC) will review and adjudicate events in a blinded manner without awareness of treatment allocation. During the study period, the ICAC will adjudicate all suspected occurrences of venous or arterial thromboembolic events, acute myocardial infarction, acute ischemic stroke, and all-cause mortality. The ICAC will also review all reported episodes of bleeding that require medical attention and categorize these events as meeting criteria for major, non-major clinically relevant, or minor bleeding. The ICAC will also review all reported hospitalization events. The ICAC will be provided with all relevant documentation related to these events. The criteria and definitions of the study outcomes as well as the procedures followed by the Committee will be described in an adjudication manual which will be provided to the ICAC members prior to the first meeting.

A2.2 *Outcome definitions*

The primary study outcome is a composite endpoint of venous and/or arterial thromboembolic events, including new, symptomatic proximal or distal DVT of the upper or lower extremities, symptomatic PE, other venous thrombotic events, ischemic stroke, myocardial infarction, and mesenteric or peripheral arterial thromboses, and all-cause mortality up to 30 days after discharge from the hospital. These endpoints are individually defined below.

Deep vein thrombosis

Deep vein thrombosis will be diagnosed by venous ultrasound or point-of-care ultrasound (POCUS) or other imaging modality, performed for clinical indications and documented in a note. A positive ultrasound test is defined by a non-compressible or partially non-compressible venous segment in an upper or lower extremity. Deep vein thrombosis may be either proximal (e.g., femoral vein) or distal (e.g., deep veins of the calf), but thrombosis of a superficial vein only does not meet criteria for a DVT.

Pulmonary embolism

Pulmonary embolism will be confirmed by chest CT using a PE protocol (CTPA), ventilation-perfusion scan (V/Q), or digital subtraction angiography (DSA), performed for clinical indications. A positive CTPA is defined as a central contrast filling defect or complete occlusion up to the subsegmental level of the pulmonary arteries. A positive V/Q is defined as at least two large mismatched segmental perfusion defects or the arithmetic equivalent of moderate or large and moderate defects (revised PIOPED). A positive DSA is defined as a filling defect or a cut-off of a vessel of >2.5 mm. Source for criteria: http://isth.breakthrough.healthcare/.

Other venous thrombotic events

Other venous thrombotic events include cerebral sinus venous thrombosis, splanchnic venous thrombosis, or renal vein thrombosis, all confirmed by appropriate imaging studies (e.g., CT angiography, MR venography) performed for clinical indications.

Ischemic stroke
Ischemic stroke will be confirmed by head CT or MRI performed for the development of new symptoms (e.g., acute hemiplegia). A transient ischemic attack is not considered an outcome for this study.

Myocardial infarction
Myocardial infarction is defined according to the universal definition of MI, which excludes myocardial injury. MI must include rise and fall of cardiac troponin above the 99th percentile with ECG changes consistent with ischemia, plus: new/presumed new wall-motion abnormalities or other imaging evidence of MI; potentially ischemic symptoms; and/or abnormal coronary angiography.

Arterial thromboembolism
Arterial thromboembolism may involve a visceral organ (e.g., spleen, kidney) or limb and must be confirmed by appropriate imaging studies (e.g., CT angiography).

All-cause mortality
Death due to any cause.

Secondary study outcomes will include venous thromboembolism (inclusive of deep vein thrombosis, pulmonary embolism, and other venous thrombotic events) and arterial thromboembolism (inclusive of ischemic stroke, MI, and other arterial thromboembolic events) up to 30 days after discharge from the hospital, as well as the primary composite endpoint, up to 45 days and 90 days after discharge from the hospital.

Hospital re-admission
Re-admission to the hospital due to any cause.

Safety endpoints
Safety endpoints will include (1) major bleeding and (2) clinically-relevant non-major bleeding, both as defined by the International Society on Thrombosis and Haemostasis (ISTH).

Major bleeding
Bleeding events that are characterized as: (1) fatal bleeding; (2) bleeding into a critical area or organ (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or (3) bleeding causing a fall in the hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells.

Clinically-relevant, non-major bleeding
Bleeding events that are characterized as: (1) bleeding requiring medical intervention by a healthcare professional; (2) bleeding leading to hospitalization or an increase in the level of care; or (3) bleeding prompting a face-to-face (i.e., not just a telephone or electronic communication) evaluation.

Appendix 3: Study Arms A and B for Stage 1

Stage 1 of this study will compare prophylactic-dose anticoagulant therapy (Arm A) to matching placebo (Arm B) on the composite endpoint of venous thromboembolism, ischemic stroke, myocardial infarction, peripheral arterial thromboembolism, or all-cause mortality. The anticoagulant therapy will be apixaban, 2.5 mg every 12 hours. The general design of the trial is provided below.

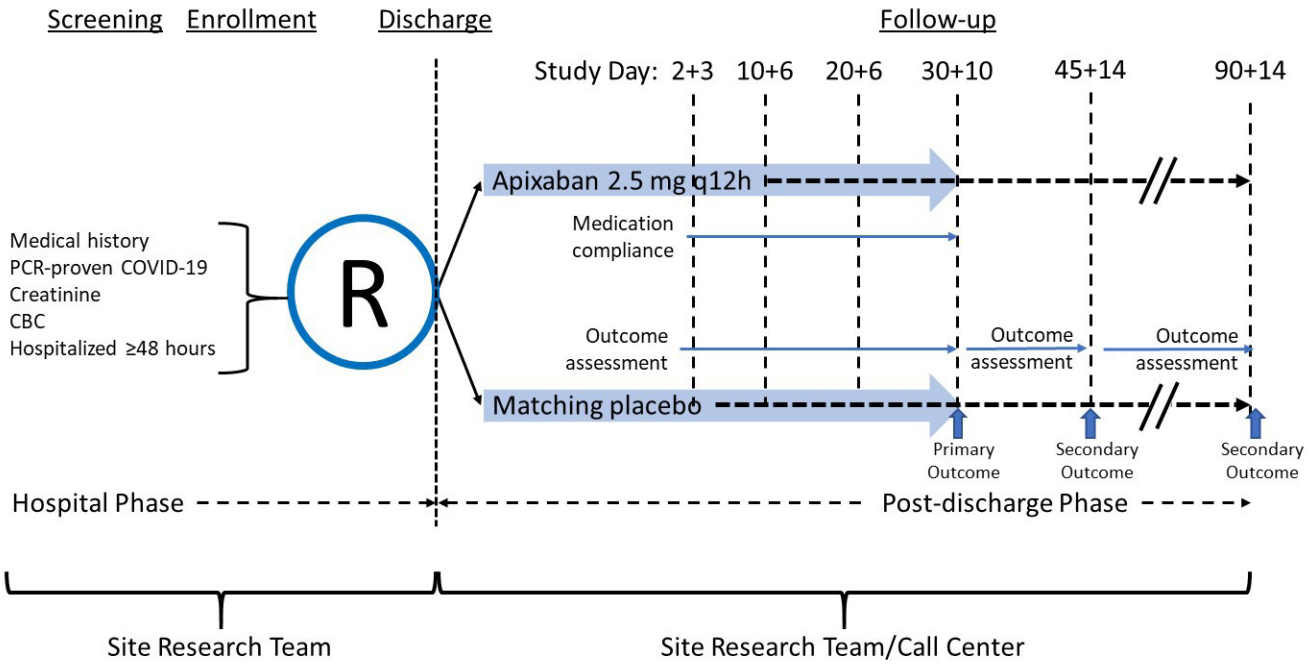

Figure 3. Stage 1 Post-Discharge Clinical Trial. Patients will be enrolled in the Study prior to discharge from the hospital and randomized to either apixaban 2.5 mg every 12 hours or matching placebo. Screening and enrollment will occur prior to discharge from the hospital, with randomization occurring as close to discharge as possible (randomization identified as the encircled "R", occurring immediately prior to discharge, identified by the vertical dashed line). Follow-up encounters for the primary outcome will occur on Days 2+3, 10+6, 20+6, and 30+10. Two additional follow-up encounters will occur for secondary outcomes on Days 45+14 and 90+14.

The trial is a prospective, randomized, double-blind, placebo-controlled trial that compares an extended prophylactic anticoagulant regimen to matching placebo. Participants randomized to Arm A will receive apixaban 2.5 mg orally twice a day for 30 days. Participants randomized to Arm B will receive a matching placebo. Follow-up encounters occur as shown in Figure 3.

This trial design will investigate whether prophylactic anticoagulation with apixaban is superior to matching placebo in this setting.

A3.1 *Potential Risks & Benefits*

A3.1.1 Known Potential Risks

Participants who use anticoagulant therapy are at an increased risk for developing hemorrhagic complications, although this risk is low in patients who are receiving a prophylactic dose of anticoagulant therapy.

A3.1.2 Known Potential Benefits

Several studies have demonstrated the importance of prophylactic anticoagulant therapy in patients with COVID-19 who are hospitalized. Although the data are currently limited, there are concerns that the increased thrombotic risk exhibited by these patients persists into the convalescent phase following discharge from the hospital. We hypothesize that the frequency of these post-discharge thromboembolic complications will be decreased with the use of a prophylactic anticoagulant.

A3.2 *Study Enrollment for Stage 1, Arms A and B*

A3.2.1 Inclusion Criteria

Inclusion criteria for Stage 1 of the protocol:

1. Age ≥ 18 years
2. COVID-19 positive test (PCR, antigen, or point of care test diagnosing a current infection) within 2 weeks of hospital admit date.
3. Hospitalized for COVID-19 infection for 48 or more hours

A3.2.2 Exclusion Criteria

Exclusion criteria for Stage 1 of the protocol:

1. Existing indication for anticoagulation, either therapeutic or prophylactic dose
2. Contraindication to antithrombotic therapy, such as
    a) ischemic stroke, intracranial bleed, or neurosurgery within 3 months
    b) Known bleeding within the last 30 days requiring emergency room presentation of hospitalization
    c) Known major surgery with 14 days (at least 1 hour and/or requires general anesthesia)
    d) Inherited or acquired active bleeding disorder
3. Platelet count < 50,000/mcL
4. Hemoglobin < 8 gm/dL
5. Renal insufficiency (eGFR < 30 mL/min/1.73 m^2)
6. Pregnancy
7. Prison inmate
8. Life expectancy less than 90 days
9. Unwilling or unable to provide informed consent/unwilling or unable to complete the study protocol
10. Dual antiplatelet therapy that cannot be discontinued
11. Concomitant need for strong inducers/inhibitors of p-gp and CYP3A4

Note that the additional exclusion criteria for dual antiplatelet therapy, and for strong inducers/inhibitors of p-gp and CYP3A4, is specific to Stage 1, since Arm A is an anticoagulant, and the anticoagulant being studied in Stage 1 is a direct oral anticoagulant.

A3.3 Safety Analyses

The rates of bleeding and thrombotic events will be summarized for each arm. For Stage 1, the rates of bleeding in Arm A, the “Anticoagulant” arm, will be directly compared to the rates of bleeding in Arm B, the “No anticoagulant” arm. If the rate of major or clinically relevant non-major bleeding in the anticoagulant arm exceeds the rate of bleeding in the no anticoagulant arm by more than 5%, this will trigger a review by the DSMB for a risk-benefit analysis of this approach.

A3.4 Treatment Regimen: Arm A

1. Prophylactic anticoagulant therapy
    - Apixaban 2.5 mg twice daily for 30 days.

    Apixaban was selected because of its documented efficacy and safety records, current usage in millions of patients, and ease of use. The prophylactic dose of apixaban (2.5 mg twice daily) was chosen because bleeding complications have been observed in patients with COVID-19 following hospital discharge and because a significant subset of the study participants will also be on an antiplatelet agent.

A3.5 Treatment Regimen: Arm B

1. No anticoagulant therapy
    - Matching placebo.

A3.6 Statistical Analyses

The anticoagulant arm (Arm A) will be compared to the matching placebo (Arm B) for efficacy on the primary outcome and the secondary endpoints, as described in Section 7 of the Master Protocol.

A3.7 Adverse Events

DEFINITIONS

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

A ***non-serious adverse event*** is an AE not classified as serious.

SERIOUS ADVERSE EVENTS

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

Any component of a serious study endpoint that is considered related or not related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

Adverse Event and Serious Adverse Event Collection Period

All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period through the 90-day visit or check-in and for a minimum of 30 days following the last dose of study treatment if the participant prematurely stops study drug.

Serious adverse events will be collected from informed consent through the 90-day visit or check-in. If the participant prematurely stops study drug, the collection will occur through a minimum of 30 days following discontinuation of dosing.

Following the subject's written consent to participate in the study, SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures.

Event Reporting

Non-serious AEs should be reported as SAEs if they become serious.

Non-serious AEs are to be provided to BMS in aggregate via the final study report as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

Serious adverse events that occur following the participant's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether or not the subject started study drug and whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

Participants can record events within an electronic patient portal. Participants can call to report an event. In addition, the Research Communication Center (RCC) is responsible for performing periodic assessments with the participants for adverse events.

If the RCC notes an unplanned medical contact by the participant (physician visit, emergency room (ER), Urgent care or hospitalization), the RCC will escalate to a pharmacist. The pharmacist will complete the Pharmacist Escalation Form within the EDC. Medical records will be obtained for hospitalizations, ER visits or if the pharmacist is unsure of potential endpoint or safety event. The coordinating center medical coordinator coordinates retrieval and upload of source documents for appropriate capture of the event(s) within the EDC. The coordinating center medical coordinator will provide the Pharmacist Escalation Form and received source documents to the coordinating center Core Medical Monitor.

The Core Medical Monitor will review the source documents to determine the event and will complete the AE/SAE form in the EDC including seriousness and causality to study drug prior for notification to DCRI Safety Surveillance.

SAEs, whether related or not related to study drug, and pregnancies must be reported to DCRI Safety Surveillance.

The Core Medical Monitors should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol- specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the Core Medical Monitor believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the AE/SAE Form in the EDC.

Upon receipt by DCRI Safety, DCRI Safety will report to BMS within 1 business day of becoming aware of the event that is determined to be an SAE. SAEs will be recorded on either CIOMS or MedWatch form. The BMS Protocol number will be included on the cover sheet with the SAE form transmission.

The Sponsor Investigator designee will reconcile the clinical database SAE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The DCRI Safety will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the DCRI Safety the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If DCRI Safety determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

In addition to the Sponsor Investigator's responsibility to report events to their local health authorities (HA), suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study participants, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

- ✓ Upon receiving an ESR from BMS, the Sponsor Investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the Sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

Follow-up

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 1 business day to BMS by DCRI Safety Surveillance using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Causal Assessment

The causal relationship to study drug is determined by a physician and should be used to assess all serious adverse events (SAE). The casual relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

13.3 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The Core Medical Monitor must immediately notify DCRI Safety Surveillance of the pregnancy via the BMS Pregnancy Surveillance Form in accordance with SAE reporting procedures.

DCRI Safety Surveillance will perform due diligence follow-up using the BMS Pregnancy Form, which the Core Medical Monitor must complete.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the BMS Pregnancy Surveillance Form if known within the study participation period. If pregnancy outcome is not known at the time of the participant's last visit of the study, BMS will follow up regarding pregnancy and neonatal outcome. A BMS Pregnancy Surveillance Form may be provided upon request. Any associated AE or SAE should be reported with the EDC.

13.4 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Appendix 4. Biospecimens

Biospecimens will be collected at two time points during the study, at the time of enrollment, and following completion of the antithrombotic therapy being studied (shortly after Day 30 for Stage 1). Samples that would collected for the biorepository would collect citrated plasma (2 tubes), serum, and a sample for genomic DNA or dried blood spot samples.

At sites capable of sample collection and processing, additional samples sent by the site teams may include: Pax gene DNA; Pax gene RNA; Platelets; and Cryopreserved PBMS.

Appendix 5. Addition of New Key Secondary and Exploratory Outcomes

A5.1 Rationale for new Secondary and Exploratory Outcomes

Health-related quality of life data has been collected on participants in ACTIV 4c by use of the EuroQol 5 Dimension 5 Level (EQ-5D-5L) survey, administered at three timepoints following randomization into the study: Day 2 (within the first few days of starting study drug), Day 30 (time of completion of study drug), and Day 90 (60 days after completion of study drug). The EQ-5D survey consists of five questions that cover the following domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The response to each question is collected as a 5-level ordinal scale, spanning scores of 1 (no problems, or best outcome), 2 (slight problems), 3 (moderate problems), 4 (severe problems) and 5 (extreme problems, or worst outcome). The rationale for collecting these quality of life data was driven by early reports describing a significant subset of patients with COVID-19 who had a prolonged course with persistent symptoms of fatigue, dyspnea, and other problems, lasting for months and longer after the acute illness.

An analysis of the EQ-5D data was not included in the Master Protocol, since study leadership had not anticipated that anticoagulant therapy would have a significant impact on quality of life. A post-hoc analysis of EQ-5D data collected in ACTIV 4a, however, comparing prophylactic-dose with therapeutic-dose anticoagulation in hospitalized patients with COVID-19 in the non-ICU setting, observed that patients randomized to therapeutic anticoagulation had less moderate-to-extreme impairment scores in four of the five EQ-5D domains at 90 days after hospital discharge. This difference was statistically significant in the self-care domain, with an improvement from 8.4% to 2.9% of participants having moderate-to-extreme impairment scores with therapeutic anticoagulation, for an odds ratio (adjusted for age, co-morbidities and pre-hospitalization status) of 0.26 (95% CI, 0.08-0.83) and a p-value of 0.016 (J. Hochman and M. Sholzberg, personal communication). This preliminary observation that anticoagulant therapy could impact quality of life in patients with COVID-19 resulted in the decision by the ACTIV 4c leadership team to include an analysis of the collected EQ-5D data in two new secondary objectives and one new exploratory objective.

A5.2 New Secondary Objectives

Secondary Objective 1: To compare the effects of treatment at 30 days after randomization for the composite endpoint of QOL and mortality.

Secondary Objective 2: To compare the effects of treatment at 90 days after randomization for the composite endpoint of QOL and mortality.

The existing three secondary objectives in the Master Protocol will now become Secondary Objectives 3, 4, and 5

A5.3 New Exploratory Objective

Exploratory Objective 3: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the individual domains of EQ5D and the EQ5D visual analog scale for 30 and 90 days after randomization.

The existing two exploratory objectives in the Master Protocol will remain as Exploratory Objectives 1 and 2.

A5.4 New Key Secondary Endpoints

The two new key secondary endpoints are:

1. The composite endpoint of EQ5D index score and mortality at day 30 following randomization

2. The composite endpoint of EQ5D index score and mortality at day 90 following randomization

The existing four key secondary endpoints in the Master Protocol will now become key secondary endpoints 3 through 6

A5.5 Secondary and Exploratory Endpoints Analyses

Six secondary outcomes are of interest in this trial. We will use a fallback method to control for type I error. Statistical methods for testing the QOL&M30 and QOL&M90 endpoints will be based on a proportional odds model. The covariates in the model will include the participant's age (restricted cubic spline with 3 knots), sex, D-dimer (normal or abnormal), BMI (restricted cubic spline with 3 knots), antiplatelet usage (yes/no - at enrollment), WHO severity score (<five vs. ≥five), and the randomized treatment. The results of these models will be summarized using an odds ratio and associated 95% confidence interval.

Secondary analyses of the QOL&M30 and QOL&M90 endpoints will use a multiple imputation approach. 20 datasets will be imputed using predictive mean matching and the above covariates plus the Day 2 and Day 90 EQ5D index scores. The model estimates will be combined using Rubin's rules to obtain the estimated odds ratio and 95% confidence interval.

More specifically, these secondary outcomes will only be formally tested if the primary hypothesis was rejected at level alpha=0.05. If the study stops without the CE30 test statistic crossing the 'efficacy boundary' or 'futility boundary' (i.e. not enough primary endpoint events), the key secondary endpoints will be evaluated and summarized using point estimates and associated 95% confidence intervals (without p-values).

The ordering of the secondary endpoints is as follows:

1) Composite endpoint of mortality and EQ5D index at Day 30 (QOL&M30)
2) Composite endpoint of mortality and EQ5D index at Day 90 (QOL&M90)
3) Primary endpoint at 45 days (CE45)
4) Primary endpoint at 90 days (CE90)
5) Venous events at 30 days (CEVTE30)
6) Arterial events at 30 days (CEATE30)

Using a fallback method the 0.05 type I error rate would be split as follows – 0.025, 0.005, 0.005, 0.005, 0.005, and 0.005. If QOL&M30 was statistically significant then QOL&M90 would be tested at 0.03 = 0.025 + 0.005. On the other hand, if QOL&M30 was NOT statistically significant then QOL&M90 would be tested at 0.005. The process would continue until all 6 secondary endpoints were tested. If the study does not accumulate enough CE30 events, it is expected that there would be limited information for secondary endpoints 3-6.

Statistical methods for testing the secondary endpoints 3-6 listed above will follow exactly the same procedures used for the primary endpoint described in Section 4.2 in the Master Protocol.

Additional details concerning the analysis of the new key secondary and exploratory endpoints are included in the Statistical Analysis Plan.

Appendix 6. Protocol Summary of Changes

Summary of Changes protocol version 4.0 to 5.0

Protocol Section	Section Name			
Title Page	N/A	Previous	Version 4.0, 20OCT2021	
		Update	Version 5.0, 20APR2022	
		Rationale	Update version	
A5	Addition of New Key Secondary and Exploratory Outcomes	Previous	NA	
		Update	All Appendix 5 is new.	