COVID-19 Outpatient Thrombosis Prevention Trial within ACTIV-4:

A multicenter adaptive randomized placebo-controlled platform trial evaluating the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalization at time of diagnosis

Sponsor: University of Pittsburgh

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ACTIV-IV COVID-19 Outpatient Thrombosis Prevention Trial

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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 Harmonisation ("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

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159 # 1 Master Protocol Summary

Title	COVID-19 Outpatient Thrombosis Prevention Trial: A Multicenter Adaptive Randomized Double-Blind Placebo Controlled Platform Trial of the Efficacy and Safety of Antithrombotic Strategies in COVID-19 Adults not Requiring Hospitalization at Time of Diagnosis
Brief Summary	An adaptive randomized double-blind placebo-controlled platform trial to compare the effectiveness of anticoagulation with antiplatelet agents and with placebo to prevent thrombotic events in patients diagnosed with COVID-19 who are not admitted to hospital as COVID-19 related symptoms are currently stable. For outpatients not meeting eligibility criteria or who decline to participate in active treatment, participation in a registry component of this trial will be available, with a single follow up 45 days from entry Biobanking of samples to assess biomarkers of inflammation and coagulation will be available for centers able to participate in collection from eligible patients.
Primary Objective	To compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) prophylactic dose anticoagulation; with (ii) therapeutic dose anticoagulation; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on the primary composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days among the study population of non-hospitalized COVID-19 patients aged $\geq$ 40 years. Assessment of efficacy and safety endpoints will yield information of the net clinical benefit of different antithrombotic strategies.

Methodology	Adaptive double-blinded randomized controlled platform trial
Endpoint	Primary Endpoint: Composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment. Key Secondary Endpoints: Individual outcomes of the composite primary endpoint, the time-to-event for the composite primary endpoint, and a clinical rank-based score. Primary Safety Endpoint: Major bleeding (as defined by the ISTH) at end of randomized therapy (45 days) and after an additional 30 days of safety follow up (day 75).
Participant Duration	45 days of assigned therapy with an additional 30-day safety follow up (i.e. a total of 75 days).
Population Key Inclusion and Exclusion Criteria	Adults age ≥ 40 and ≤ 80 years found to be COVID-19 positive who do not require hospitalization due to stable COVID-19 related symptoms status. Participants will be enrolled from a variety of different facilities where (a) a clinician can evaluate the patient for inclusion and exclusion criteria, and (b) where blood samples can be arranged to be sent for D-dimer, hsCRP, calculated creatinine clearance, and platelet count. COVID-19 testing needs to be confirmed positivet within the past 14 days.. Serum or urine pregnancy test results will be required for women of childbearing potential before starting study treatment. Patients with a contraindication to or requirement for anticoagulant/antithrombotic therapy are not eligible.
Study Sites	Approximately 100 sites

Number of participants	The estimated sample size is approximately 7000 subjects. However, incorporating an adaptive design strategy will alter the final number of enrolled subjects.
Initial Description of Study Agents (Stage 1)	Stage 1 is a four-arm trial incorporating: 1. Anticoagulation: prophylactic dose apixaban 2.5mg po bid 2. Anticoagulation: therapeutic dose apixaban 5.0mg po bid 3. Antiplatelet agent: low dose aspirin 81mg po qd 4. Placebo For trial efficiency and to maintain blind, all participants will be shipped via overnight courier two pill bottles with supply sufficient for the 45 day trial duration. For participant simplicity and to improve adherence and compliance, the bottles will be labeled “A-AM” and “B-PM” with the appropriate distribution of the above active agents and matching placebos. As such, all participants will be taking two identical appearing pills daily, regardless of randomized study arm assignment. An Adaptive Design will be used to drop or add arms in subsequent Stages.
Key Procedures	See Stage-specific Appendix
Adaptive Design Considerations	A modified intention-to-treat approach including only subjects who begin treatment will be used for primary trial analyses. The adaptive design embedded in this platform trial calls for evaluations of safety and efficacy overall and across multiple strata of admission D-dimer as well as admission hsCRP. In-trial data and specified decision rules will be used by the DSMB to suggest discontinuation of a specific trial arm due to safety concerns or clear evidence of efficacy or futility, thus allowing the trial to drop antithrombotic or anticoagulant agents or to add alternative therapies during the course of the trial (Stages 2 and beyond). Additional adaptive protocol issues will require DSMB evaluation including duration of therapy based on the timing of outcome events, both beneficial and potentially hazardous.

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2 INTRODUCTION

2.1 Background information, significance, and relevant literature

The COVID-19 pandemic has resulted in worldwide disruption in everyday life. Physicians accustomed to practicing evidenced based care are now faced with clinical situations for which no data are available to guide care.

The inflammatory response of most patients to infection with SARS-CoV2 is significant, with elevation in proinflammatory cytokine levels such as Il-6 and others, resulting in dramatic elevations in inflammatory biomarkers such as ESR and CRP. [1,2,3,4,5,6] The crosstalk between the coagulation system and activation of inflammatory pathways results in cytokine driven increases in procoagulant proteins such as fibrinogen, and activation of coagulation through numerous mechanisms including polyphosphates, NETs, and contact activation of the intrinsic pathway of the coagulation system. This significant inflammation in patients with SARS-CoV-2 infection has been demonstrated with elevated levels of IL-6, increased CRP and ESR, and elevated fibrinogen and changes in coagulation tests results such as D-dimer and PT, even at initial presentation.[7] Given the tropism of the virus for ACE2 receptors, endothelial cells are a target. Direct viral infection of vascular endothelial cells results in apoptosis and loss of the normal protective antithrombotic environment provided by a number of natural anticoagulant activities.[8] The loss of the protective effect of vascular endothelial cells has been implicated in the development of microvascular thrombosis, especially in the alveolar capillaries as found on autopsy. [9] In addition, vascular endothelial cell activation and cell death leads to release of VWF, with high circulating levels adding to the procoagulant milieu. Recent data suggest that platelets may also play a role in the pathophysiology of COVID-19, with altered gene expression and platelet hyperreactivity noted in patients infected with SARS-CoV-2. [10] The aggregate effect of this increased inflammation and destruction of host cells is to produce a hypercoagulable phenotype in infected patients with risks for microvascular and macrovascular venous and arterial thrombotic events.

Early data from Wuhan noted marked elevation in fibrinogen levels, inflammatory cytokines, and D-dimer levels, and noted that D-dimer tracked with mortality.[3,4]

Evidence of abnormal coagulation parameters associated with COVID-19 appeared in early reports from China. Baseline characteristics of the first 99 patients hospitalized in Wuhan found that 6% had an elevated aPTT, 5% elevated PT, 36% elevated D-dimer, increased biomarkers of inflammation including interleukin-6 (Il-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). [2] Additional reports from another Wuhan hospital on the first 138 patients found minimal elevations in PT and normal aPTT, but elevated D-dimers.[3] In an analysis of 191 patients from 2 of the main Wuhan hospitals, mortality was reported to be 28% (54-patients).[19] Factors associated with mortality included an elevated D-dimer > 1.0 mcg/mL on admission, increased PT, elevations in IL-6, and other biomarkers of inflammation, elevated troponin levels, and co-morbidities including older age, hypertension, diabetes, and coronary artery disease. Approximately 50% had evidence of coagulopathy defined as a 3-second PT increase or a 5-second increase in aPTT. In a multivariable logistic regression model of 171 patients, a D-dimer level greater than 1.0 mcg/mL at admission was associated with increased mortality with an OR of 18.42 (2.64-128.55, p=0.003). [4]

Following these early reports from China, data from other countries have substantiated the marked inflammation, elevated levels of procoagulant proteins, and inflammatory markers, and the association of increased D-dimer with more severe infection. [6,11,12,13,14] Multiple reports indicate an increased incidence of venous thromboembolism in COVID-19 positive patients, especially in those requiring ICU care, with cumulative incidences of symptomatic VTE roughly 25% at 14 days despite the use of VTE prophylaxis, higher than historic VTE incidence in ICU patients. [11,13] Even when compared to similarly critically ill patients with ARDS or with influenza infection.[12,14] Use of surveillance ultrasound screening results in an even higher frequency with up to 70% of patients found to have VTE. [15] Arterial events including MI, ischemic stroke, and limb arterial thrombotic events occur, although much less frequently than venous.[11]

Although the incidence of VTE in COVID-19 positive patients that do not require hospitalization at time of diagnosis has not been identified, PE found on autopsy reports have been believed to be the cause of death in patients never hospitalized who died at home.[16] Speculation about the current higher death rates than in past time matched periods in many cities with high prevalence of COVID-19 has centered on a multitude of possible COVID-19 related causes including PE. Many patients are diagnosed with VTE at the time of presentation to the emergency room, after having been symptomatic at home with COVID-19; PE may be a possible cause for sudden worsening of symptoms prompting medical attention. In a French review of CTPA performed on 137 patients presenting from home with respiratory symptoms attributable to either pneumonia or PE, 23% of scans obtained in the emergency room were positive for PE, all were confirmed to have COVID-19. [17] Another similar evaluation found that PE were present in 18% of CTPA performed in the ER for outpatients ultimately diagnosed with COVID-19.[18] A US center found that 22% of patients presenting to the ER with respiratory complaints and eventually diagnosed with COVID-19 also had PE on CTPA.[19] Pulmonary microvascular thrombosis may also be responsible for the significant hypoexemia seen in COVID-19 positive patients.

It is clear that patients with COVID-19 have marked inflammation and a hypercoagulable state that leads to venous and arterial thrombotic events, including microvascular thrombosis, and may contribute to pre-hospital mortality in patients infected with COVID-19. The appropriate strategy to prevent pre-hospital events is not known.

We propose an adaptive double-blind randomized placebo-controlled platform trial to compare the effectiveness of anticoagulation with antiplatelet agents and with placebo to prevent thrombotic events in patients diagnosed with COVID-19. Available data demonstrate that both D-dimer levels and CRP levels can be used to select patients at higher risk for thrombotic events as part of a risk stratification score. [20] Patients diagnosed with COVID-19 not requiring hospitalization, ie those meeting criteria for WHO COVID-19 ordinal score of 1-3, will be

randomized initially to one of four strategies: placebo, low dose antiplatelet agent with low dose aspirin 81 mg, prophylactic dose anticoagulation with apixaban 2.5mg po bid, or therapeutic dose anticoagulation with apixaban 5.0 mg po bid. D-dimer and CRP are key variables that will be used to create patient subgroups since we hypothesize that the treatment effect on the primary outcome (and safety outcomes) may vary based on D-dimer or CRP level. The primary outcome will be a composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days. The trial will adhere to adaptive design principles, with modifications of a number of variables based on evaluation of accrued in-trial data to inform the progressive shift in antithrombotic strategies towards the superior therapy. For example, should the therapeutic dose apixaban arm prove hazardous without greater benefit, this anticoagulant arm could be terminated early. In addition, if primary endpoint event rates are extremely low for patients with normal D-dimer and CRP, eligibility criteria may be modified to exclude this group of patients. These changes will be made through use of a pro-active DSMB structure in which the investigators are not directly involved in the formal decision-making process, thus maintaining overall trial integrity.

2.2 Therapeutic agent rationale, potential benefit, potential risk

The initial antithrombotic agents to be used in Stage 1 of this trial have been chosen for their potential for efficacy to reduce thrombotic events in COVID-19 patients not requiring hospitalization based on supporting efficacy data from clinical trials and ease of use in the outpatient setting. Risks associated with the use of the antiplatelet agent aspirin and anticoagulant treatment apixaban are primarily bleeding, with data available from a multitude of studies demonstrating low rates and acceptable safety profiles as described below, especially when one considers the 45 day treatment period.

Apixaban is an orally active, direct selective inhibitor of the coagulation factor Xa (FXa) developed by Bristol-Myers Squibb Company (BMS) and Pfizer as an anticoagulant agent. In

adults, apixaban has been administered orally (PO) as single and multiple doses of up to 50 mg and intravenously (IV) as single doses of up to 5 mg; the majority of subjects have received apixaban PO. Apixaban is authorized for marketing in 103 countries worldwide, including the European Union (EU), United States (US), and Japan. In the US, apixaban is approved in adults for the following: Reduction in the risk of ischemic stroke and SE in patients with NVAF, prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery, treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. In the EU, apixaban has similar use indications.

For Stage 1 of the trial, in two of the arms, patients will be randomized to either the prophylactic dose of apixaban 2.5 mg po bid or to the therapeutic dose of apixaban 5 mg po bid for 45 days. Data from the AMPLIFY-Extension trial comparing the use of these 2 doses of apixaban with placebo for secondary VTE prophylaxis in high risk patients over 12 months noted similar reduction in recurrent VTE with both apixaban doses compared with placebo, with 63% and 67% reductions in the primary endpoint of recurrent VTE or all-cause mortality.[21] Neither dose of apixaban increased the rate of major bleeding compared to placebo. Major bleeding rates were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group, with rates of clinically relevant non-major bleeding of 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group, and 4.2% in the 5-mg apixaban group. The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group.[21] In subsequent stages of the trial, the adaptive design with pre-determined analyses of in-trial accrued data may drop individual treatment arms or change the duration of therapy for apixaban in response to findings of efficacy and safety.

While aspirin at 81 mg or 100 mg has a long track record of prevention of arterial thrombotic events [22,23,24] it also has demonstrated efficacy at reducing the risk of recurrent VTE as demonstrated in the WARFASA and ASPIRE trials. [25,26] High risk patients similar to those enrolled in the APMLIFY-Extension trial demonstrated over a 30% risk reduction in recurrent

VTE compared to placebo. Recent studies and meta-analyses suggest that aspirin is also effective in primary prevention of VTE, and has been shown to be as effective as other agents in post joint arthroplasty patients. The RR of VTE after hip and knee replacement surgery was 1.12 (95% CI, 0.78-1.62) for aspirin compared with other anticoagulants. [27] The safety profile of low dose aspirin was demonstrated by the extremely low major bleeding rates in these trials, with only 1 major bleed in 205 patients taking aspirin and 1 major bleed in the 197 patients taking placebo in the WARFASA trial over a median duration of 24 months on treatment. [25] However, the utility of low dose aspirin in the setting of outpatient COVID-19 is unknown.

Recently diagnosed and symptomatic COVID-19 patients will be eligible for the main trial if they have no contraindications to anticoagulation or anti-thrombotic therapy. As described below, the pre-specified analysis plan will address the net benefit to risk ratio of antithrombotic and anticoagulant strategies across ranges of D-dimer and hsCRP at baseline.

For patients not meeting eligibility criteria for enrollment into the active treatment/placebo trial, enrollment in a companion registry trial can be offered. The registry will prospectively collect data in parallel with the active treatment trial, evaluating similar outcomes and obtaining useful information to inform further investigation.

In summary, the proinflammatory and procoagulant state with resultant thrombotic events associated with COVID-19 indicate a need to address the thrombotic risks of infected patients in the outpatient setting. There is equipoise regarding the best strategy for preventing thrombotic events among patients with confirmed SARS-Cov-2 infection not requiring hospitalization. The trial addresses this need with a double-blinded randomized placebo-controlled platform trial initially evaluating apixaban compared to aspirin using an adaptive design to allow assessment of accrued in-trial data to maximize the results and generate answers to current management questions that have developed during this pandemic and for which no answers currently exist.

3 Study Design

3.1 Overall study design

This platform trial features multiple adaptive design elements inclusive of approaches to early stopping and changes in intervention based on accrued in-trial data. As such, the design is intended to adapt to new information as it becomes available in this rapidly evolving clinical and research environment, with updates to the design and execution. This trial is also designed to be flexible in this rapidly evolving clinical and research environment, and incorporates the ability to rapidly update the design and execution as new information on the science and understanding of COVID-19 pathology and the role of standard of care and treatment modalities becomes available. Each period of the study where intervention arms are added or dropped will be considered a separate study Stage.

3.2 Primary Endpoint

The primary endpoint, analyzed as a binary outcome, is the composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned therapy. All events suggestive of the primary outcome will be adjudicated by an independent Adjudication Committee.

3.3 Randomization

Initial Stage 1 randomization assignments will be performed for patients at baseline. Subjects will be randomized (1:1:1:1 ratio) to apixaban 2.5 mg bid, apixaban 5 mg bid, aspirin 81 mg qd + placebo, (Groups 1 to 4 as in the table below using a centralized service). A permuted block

design, stratified by country, will be used to allocate equal numbers of participants to each of the four designated interventions included in the current study stage.

3.4 Study Stages and Interventions

The first Stage of this study has been determined and is outlined above. In Stage 1, there will be four intervention arms: (1) prophylactic anticoagulation with apixaban 2.5mg po bid; (2) therapeutic anticoagulation with apixaban 5.0mg op bid; (3) antiplatelet therapy with low dose aspirin 81mg po qd and (4) placebo. Subsequent Stages will incorporate recommendations from the DSMB based on the accrued in-trial data at pre-specified time-points or from a pre-specified number of patient events to adjust criteria for eligibility, assignment to treatment groups, and endpoints, and could include any combination of these.

At the outset of the trial, the overarching plan for adaptive changes are as follows:

1. **If an active drug is found to be futile relative to placebo** (i.e. results indicate that an active arm is associated with a slightly reduced risk, no effect, or a greater risk of the primary outcome as compared with placebo): The futile active arm will be dropped, no new treatment arm will be added, and the trial will continue with the remaining treatment arms. The randomization scheme will be adjusted to include the 3 remaining arms with equal probabilities (i.e. 1:1:1), and the treatment comparisons among these arms will continue as designed.

2. **If an active drug is found to be superior to placebo**: We will declare a winner, and we will announce this finding. The placebo arm will be dropped. If the observed differences between the superior active arm and all of the other active arms are sizable (e.g. >20% relative reduction) but do not yet cross the decision boundary, the trial may be terminated based on a risk/benefit analysis by the DSMB. If the observed differences between the superior active arm and at least one of the other active arms is small, this would be announced, and the trial may continue with the “competitive arms” based on a risk/benefit analysis by the DSMB. The randomization scheme will be modified to assign each of the remaining treatment arms with an equal probability. The aspirin arm will become the reference arm for future statistical models.

3. **If a promising new drug is identified from external studies**: At the outset of this trial, we do not plan on adding any new treatment arms. An anti-platelet drug and two doses of anticoagulant (prophylactic and therapeutic) were selected as the best candidates for treating COVID-19 in an outpatient setting based on the current available evidence. However, if a promising candidate drug were to be identified in the next 6 months, we will consider adding an arm to the trial based on time and other pragmatic considerations. The randomization scheme and analytic approach would be modified to include an extra treatment arm.

3.5 Registry

For subjects not meeting eligibility criteria for enrollment into the active treatment/placebo trial, or those declining enrollment in active treatment, enrollment in a companion registry will be offered. The registry will prospectively collect data in parallel with the main trial, evaluating similar outcomes and obtaining useful information to inform further investigation. All demographic and baseline characteristics will be collected as for participants in the active treatment trial, however laboratory assessments will not be performed. Follow-up assessment by electronic communication or telephone will occur at 45 days, with screening for the same outcome events as for the active treatment trial.

3.6 Biobank

The ability to biobank samples for further studies of biomarkers of inflammation and coagulation will be part of this trial. Centers with the capability of collecting, processing, and shipping samples can opt in for biobanking and collecting these samples from eligible and consented patients.

4 Objectives and Purpose

The overarching objective of this adaptive research design is to iteratively learn which therapeutic strategy is the best in COVID-19 patients presenting to an emergency department or other appropriate healthcare facility capable of performing all required assessments but not requiring hospitalization (WHO COVID-19 ordinal score 1-3) at time of diagnosis for the primary, secondary, and safety outcomes. At each Stage of the trial, we will identify the superior therapy that should be considered standard level of care for this population. The subsequent stage will introduce an alternative strategy and design that will be compared to this new standard of care in a similar fashion. This process will continue until no new strategies replace the standard of care.

4.1 Primary Objective – Stage 1

The primary objective is to determine the rate of the composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment.

Objective 1: To compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on the primary composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment among the study population of non-hospitalized COVID-19 patients aged $\geq$ 40 years.

4.2 Secondary Objectives – Stage 1

Objective 2: To compare the effects of treatment in the outpatient setting with (i)

anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; (iii) with antiplatelet therapy; and with (iv) placebo relative to each other on need for hospitalization for cardiovascular/pulmonary events .

Objective 3: To compare the effects of treatment in the outpatient setting with (i)

anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; (iii) with antiplatelet therapy; and with (iv) placebo relative to each other on the diagnosis of venous thromboembolism including symptomatic DVT and PE.

Objective 4: To compare the effects of treatment in the outpatient setting with (i)

anticoagulation at prophylactic doses; with ii) anticoagulation at therapeutic doses; (iii) with antiplatelet therapy; and with (iv) placebo relative to each other on arterial thrombotic events including MI, ischemic stroke, and arterial thromboembolism.

Objective 5: To compare the effects of treatment in the outpatient setting with (i)

anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; (iii) with antiplatelet therapy; and with (iv) placebo relative to each other on all-cause mortality.

Objective 6: To compare the effects of treatment in the outpatient setting with (i)

anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; (iii) with antiplatelet therapy; and with (iv) placebo relative to each other on the endpoint of mortality without antecedent hospitalization.

Objective 7: To compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on the time-to-the primary composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality over 45 days after initiation of assigned treatment among the study population of non-hospitalized COVID-19 patients aged ≥ 40 years.

Objective 8: To compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on a clinical rank-based score over 45 days after initiation of assigned treatment among the study population of non-hospitalized COVID-19 patients aged ≥ 40 years.

Objective 9: To compare the effects of treatment in the outpatient setting of the (i) combined prophylactic and therapeutic doses of apixaban with (ii) placebo for the primary endpoints for efficacy and for safety**.**

Beyond these primary aims, a major interest of the trial is to address the net benefit-to-risk ratio for oral anticoagulation and oral antithrombotic therapy as compared to placebo across increasing thresholds of D-dimer and across increasing thresholds of hsCRP. These analyses will be pre-specified in the Statistical Analysis Plan and are part of the adaptive design of the overall trial; for example, should either net benefit or net risk relate to baseline levels of D-dimer or hsCRP in Stage 1, the DSMB (following guidelines established a priori by the investigative team) may indicate that thresholds for these biomarkers be selected going forward into new stages.

4.3 Safety Objective

To compare the effects of treatment with (i) with prophylactic dose anticoagulation with (ii) therapeutic dose anticoagulation and with (iii) antiplatelet therapy, both relative to placebo alone, on bleeding among the study population. Bleeding will be defined as (1) ISTH major or (2) ISTH clinically relevant non-major bleeding (CRNMB).[28] The development of disseminated intravascular coagulation (DIC) will also be evaluated. These will be analyzed at end of randomized therapy (45 days) and after an additional 30 days of safety follow up (day 75).

5 STUDY DESIGN

This trial design is built as a platform process with the possibility of multiple interventions being investigated iteratively over time. The trial is designed to be flexible, and these flexible aspects are planned as part of the protocol. This trial may incorporate a flexible number of interventions, and the number of interventions may evolve as the science evolves. Each period of the study where intervention arms are added or dropped will be considered a separate study *Stage*; the trial's analysis, however, will incorporate all Stages simultaneously via a single comprehensive model. An adaptive trial design will allow for "in-flight" changes to the protocol based on real-time data. Areas in which an adaptive design will be critical include the possible need to shorten the length of therapy depending on the timing of events, discontinuation of ineffective or unsafe treatment arms, changing antiplatelet or anticoagulant strategies, or adding new agents based on emerging science and data. We will also correlate outcomes with D-dimer and hsCRP levels evaluated at baseline, and patient characteristics/ demographic factors, in an ongoing manner to inform adaptation of entry criteria and treatment arms as needed.

5.1 Stage 1

The Stage 1 study is designed as a double-blinded randomized controlled platform trial of COVID-19 positive patients presenting to an emergency department, other appropriate health care facility, or research call center capable of performing or arranging for all required assessments. Participants will be recently diagnosed with symptoms (WHO COVID-19 ordinal

score 1-3) and age ≥ 40 years. In Stage 1, willing and able participants will initially be randomized to i) prophylactic anticoagulation with apixaban 2.5mg po bid (ii) therapeutic anticoagulation with apixaban 5.0 mg po bid; (iii) antiplatelet therapy with aspirin 81mg po qd or (iv) placebo in a 1:1:1:1 ratio.

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Participants can be identified either in emergency departments or in appropriate healthcare facilities capable of performing all required assessments and perform or confirm COVID-19 test results. In addition to emergency department settings, these can include COVID-19 testing sites within hospitals such as adjacent tents, urgent care centers, and similar medical care facilities that have the ability to obtain CBC, creatinine, D-dimer, and CRP data at the time of COVID-19 testing or with verification of positive SARS-CoV-2 PCR or antigen test within the past 14 days, pathway 5.1.1 A. Free standing test sites that identify positive patients can refer to central study staff of the research call center who will be able to determine eligibility based on criteria as described in section 6, Study Population, screen for the inclusion and exclusion criteria of the trial, and perform assessments and laboratory values described in section 7, see pathway 5.1.1 B below. Hybrid models using a combination of steps for SARS-COV-2 testing, lab draws, consent and randomization from both ED/urgent care and freestanding test center pathways can be used as in 5.1.1 C. All participants must be able to have blood drawn for CBC, creatinine, D-dimer, and hsCRP; this can be performed by home health clinician visits or clinical facility and does not have to have performed at the time of the initial SARS-CoV-2 test. Test results do not have to be available prior to randomization but laboratory tests must be drawn prior to starting study treatment. Serum or urine pregnancy test results in WOCBP need to be known prior to starting study treatment.

All trial follow-up will be conducted directly from the Coordinating Center with the trial participants themselves using electronic contact and / or call center telephone contact on a regular basis over the planned 45-day treatment period and the additional 30 day safety follow up period. All double-blind trial medications will be packaged in child-proof containers and will be directly shipped on an overnight basis across the USA to the participants home address (see section 8, Study Agent) to maximize efficiency and minimize waste of study drug at centers not aggressively enrolling.

The overarching intent of this trial design is to minimize subject contact and minimize on-site in person study visits, given logistical considerations for social distancing during the COVID-19 pandemic. Potential participants who are likely COVID-19 positive but not requiring hospitalization will be identified at participating sites. The study clinician will complete a set of inclusion and exclusion screening criteria through patient interview., Screen-eligible patients will be given information regarding participation in the trial. This may include a combination of in-person communication and video technology that describes the trial in layman's terms.

5.1.1 Pathways for enrollment

A. **ED, urgent care**: and other clinic sites capable of performing screening and all laboratory tests at the first visit can consent participants at this one visit and in person if participants meet eligibility criteria, and positive COVID-19 test results available from that day or within the past 14 days or pending. Laboratory tests can be drawn at this time and results can be evaluated before or after randomization.

Study medication will be shipped after randomization. Test results will be entered into the EDC; serum or urine pregnancy test results must be known before participant starts study treatment. Results returning after randomization that disqualify the participant for eligibility will be handled as below in 5.1.2. Follow schedule of assessments A.

B. **Free-standing test centers** that identify symptomatic COVID-19 positive patients will call those patients that agreed at the time of testing to be contacted for possible participation in ACTIV-4b if the test is positive. Test center affiliates will perform brief screening and will transfer the patient to central clinical pharmacy study staff at the research call center, who will confirm interest and eligibility by telephone and perform electronic consent. Participants will then be randomized, drug will be shipped, and arrangements for home health RN visit with blood draw will be made. Participants will be instructed not to start medication until after blood draw occurs and serum or urine pregnancy test results, if applicable, are known. Lab results will be entered into the EDC. The home health visit RN will perform education and tell participant when to start treatment. Laboratory results returning after randomization that disqualify the participant for eligibility will be handled as below in 5.1.2. Follow schedule of assessments B.

C. **Hybrid sites**: Sites that can identify symptomatic COVID-19 positive patients diagnosed within the past 14 days from any testing source or distribution list, such as affiliated ED or clinics, or free-standing test centers, can arrange for in person or remote visits to perform screening and baseline evaluation and arrange for required laboratory testing. Consent can be performed in person or remotely by electronic consent methods following the same procedure in 5.1.1 A or 5.1.1 B by site staff. Laboratory tests can be drawn before or after randomization, using on site laboratory testing, off-site laboratory testing, or home health visits. Drug will be shipped after randomization. Participants will be instructed on when to initiate study treatment after randomization; laboratory tests must be drawn before starting

treatment. Test results will be entered into the EDC. Serum or urine pregnancy test results must be known before participant starts study treatment. Results returning after randomization that disqualify the participant for eligibility will be handled as below in 5.1.2. Follow schedule of assessments A if drawing lab tests before randomization or B if drawing after randomization.

D. Sites can enroll subjects in the registry component if the participant declines to participate in the active drug trial. Participation in the biobank component if available at the site will be offered at the time of consent.

5.1.2 Test results: If a participant is randomized before laboratory test results have returned, results will be entered into the EDC by the site or by electronic transfer from the test facility. Laboratory tests obtained after randomization must be entered within 72 hours of blood draw. Follow up contact of participants who do not meet eligibility requirements will be performed by enrolling sites if using the ED or hybrid site pathway or research call center pharmacist.. Participants will be told to stop treatment and given instructions to return unused study drug. These participants will be followed for all efficacy and safety events for 45 days and for the 30 day safety evaluation, and they will be included in the mITT analysis if they had initiated treatment and have at least one follow-up visit . A follow-up visit includes a contact where patient-reported outcomes or site-reported outcomes about patient status are collected.

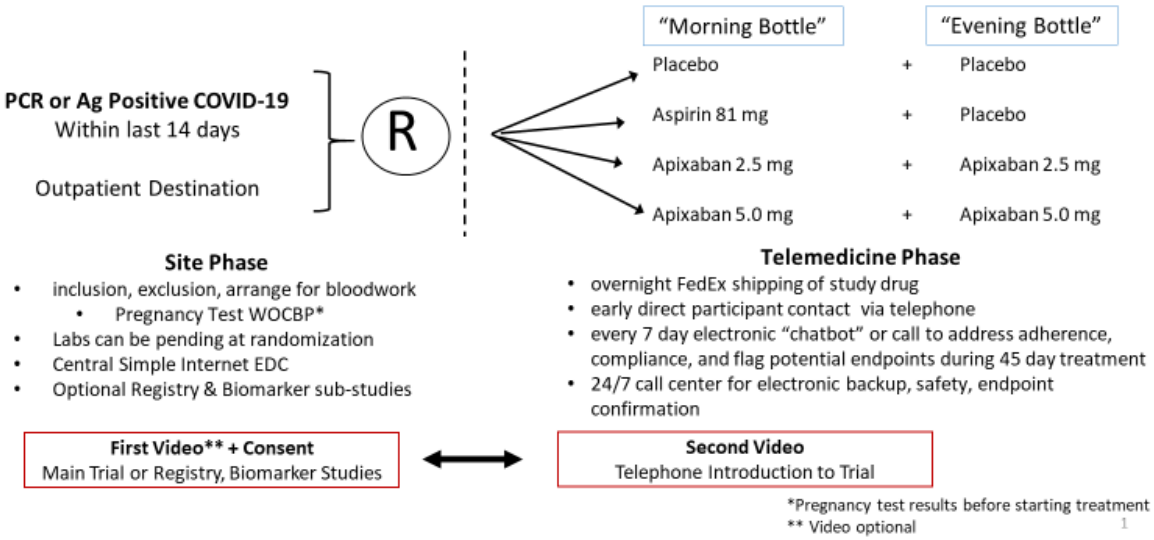
5.1.3 Review of inclusion and exclusion criteria by the consenting clinician will be performed to ensure that patient's condition is stable and all criteria are correct. Patients consenting for the treatment trial will have data registered in the EDC and will be randomized via a secure Internet Web-based Randomization System (IWRS) in eSOCDAT according to the schema in Table 5-1.

5.1.4 For efficiency of drug distribution, participants will be supplied with investigational study drug in child-proof bottles labeled “Bottle A-AM” and “Bottle B-PM” via overnight shipping directly to addresses as confirmed by the subject (see section 9). The apixaban arms will have active drug in the AM and PM bottles, the aspirin arm will have active drug in the AM bottle and matching placebo in the PM bottle, and the placebo arm will have matching placebos in both the AM bottle and in the PM bottle.

*Table 5-1 – Study **Treatment arms***

Group	treatment	Dose AM	Dose PM	Duration
1.	Apixaban	2.5 mg	2.5 mg	45 days
2.	Apixaban	5.0 mg	5.0 mg	45 days
3.	aspirin	81 mg	placebo	45 days
4.	placebo	Placebo	placebo	45 days

Figure 5-1 – Study flow and randomization



Study drug will be shipped over night to the participant as described in section 9 below. Subjects will be contacted either electronically or by telephone within 24 hours of randomization to confirm receipt of the study treatment. Receipt of study treatment will also be tracked using the shipping courier's tracking system. Detailed directions will be given to the subject at that time, with written dose instructions accompanying study drug reinforced with electronic and verbal discussion by central study staff. Information about the trial will also be provided on an insert for the patient to give to their local healthcare provider. If there is documentation of delivery but no response from the subject, study staff will contact the subject by telephone within 24 hours.

It is anticipated that subjects will start the assigned study treatment within 24-36 hours after randomization. A modified intention-to-treat (mITT) approach will be used such that only subjects who take at least one pill of study medication and have at least one follow-up visit. A follow-up visit includes a contact where patient-reported outcomes or site-reported outcomes

about patient status are collected. will be included in the analysis, and trial follow up will begin at the time of treatment initiation

Subjects will be contacted (electronic or telephone) minimally weekly after initial start of study medication for 45 days with a following 30 day safety assessment at day 75 after starting study treatment.. Follow up electronic contact will be dependent on initial patient response, compliance with response, and medication adherence, for the trial duration using electronic contacts and through telephone contacts. Participants will be queried for any clinically relevant endpoints, especially major bleeding, or need to seek healthcare attention for any reason. Follow-up will occur from the time of study drug receipt and through the 30 day safety period.

5.2 Duration of study participation

For all enrolled subjects, treatment duration will be 45 days unless a primary, secondary, or safety outcome occurs before 45 days. The trial follow-up will continue for 45 days after treatment initiation, and there will an additional 30 day follow-up (i.e. through day 75) for the collection of safety outcomes .

5.3 Primary study endpoint

The primary endpoint will be a composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment.

5.4 Secondary study endpoints

Key secondary endpoints of treatment effects are the individual components of the primary composite i.e.:

- Hospitalization for cardiovascular/pulmonary events
- Death occurring without antecedent hospitalization

- Symptomatic DVT
- Pulmonary embolism
- Arterial thrombotic events including MI, ischemic stroke, other arterial thromboembolism
- All-cause mortality

The time-to-event for the composite primary endpoint up to 45-days will be considered a key secondary endpoint.

In addition, a clinical rank-based score will be created based on events occurring during the 45-day treatment period. The score will incorporate the occurrence of efficacy and safety events. The following numeric rankings will be used to order patient outcomes from best (score=1) to worst (score =9):

1. No clinical event (i.e. no study endpoint, safety endpoint or urgent/emergent health care encounter)
2. Non-fatal bleeding that does not require an urgent care center visit, emergency room visit or a hospital admission
3. Non-fatal event that is one of the composite primary events that requires an urgent care center visit or emergency room visit but not a hospital admission (e.g. this includes a DVT or pulmonary embolism that do not result in a hospital admission)
4. Non-fatal hospitalization for bleeding event or cardiovascular/pulmonary event not including stroke, MI, pulmonary embolism or DVT.
5. Non-fatal hospitalization for DVT
6. Non-fatal hospitalization for PE
7. Non-fatal hospitalization for MI
8. Non-fatal hospitalization for stroke
9. Death

All trial efficacy analyses will include events that occur during the 45 day treatment period.

5.5 Safety end points

Safety endpoints to be evaluated throughout the 45 days of assigned treatment and during the additional 30 day follow up safety period will include:

- Major bleeding (ISTH major bleeding)
  - Drop in hemoglobin of 2 gm/dl attributed to bleeding and
  - Requiring transfusion of 2 or more units
  - Bleeding in a critical site which includes hemorrhagic stroke and intracranial hemorrhage
  - Fatal bleeding
- Mild bleeding (ISTH CRNMB)

  Non-major clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study intervention, or associated with discomfort for the participant such as pain or impairment of activities of daily life.

  - Development of disseminated intravascular coagulation (DIC)

Safety analyses will include events that occur during the 45 day treatment period and the additional 30 day post-treatment period.

5.6 Adjudication of events

As this trial will be conducted in the outpatient setting with remote and telephone monitoring of patient and patient reporting of events and hospitalizations, patient reported events will be

investigated by the Coordinating Center, including obtaining source documentation information from healthcare facilities where patients received treatment. An independent central adjudication committee (ICAC) at Brigham and Women's Hospital 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 the primary outcome composites. The ICAC will also adjudicate all suspected episodes of bleeding including hemorrhagic stroke and intracranial hemorrhage and categorize adjudicated bleeding as major or clinically relevant non-major. Bleeding events classified as minor by the RCC and confirmed by the Medical Monitor team to be minor will not be sent for adjudication. The ICAC will also adjudicate cause-specific hospitalization. The Committee will be provided with all relevant source documentation related to the events. The criteria and definitions of the study outcomes as well as the procedures followed by the ICAC will be described in an adjudication manual and endpoint charter.

6 Study Popualtion

6.1 Inclusion Criteria

Stage 1 inclusion criteria are listed below. Age and biomarkers are used to select patients at higher risk of thrombosis for anlaysis. Per the adaptive trial design strategy, these criteria may change after the first and subsequent analyses of in-trial accrued data.

- Age between 40 and 80 years inclusive
- Documentation of PCR or antigen test positive symptomatic COVID-19 infection in the past 14 days
- ability to be contacted by telephone or other electronic methods of communication
- negative pregnancy test for WOCBP

6.2 Exclusion Criteria

Stage 1 exclusion criteria are listed below, subject to change based on adaptive trial design and analyses of in-trial accrued data.

- Indication for therapeutic anticoagulation (mechanical heart valve, AF, APS)
- Indication for single or dual antiplatelet therapy
- lactating
- primary brain tumor or acute leukemia
- bleeding risk:
  - hospitalization in the past 2 months for:

    bleeding due to ulcer or GI tract disease

    major surgery, stroke, or intracranial hemorrhage
- platelet count < 100,000 per microliter can be obtained after randomization
- calculated creatine clearance < 30 ml/min can be obtained after randomization
- ever hospitalized after diagnosis of COVID-19
- concomitant need for strong inducers/inhibitors of p-gp and CYP3A4 (17: Appendix B)
- SARS-CoV-2 PCR or antigen test more than 14 days prior
- Unable to give written informed consent

See section 5.1.2 for management of laboratory test results

6.3 Total Number of Participants

Sample size calculations can be found in section 11 Statistical Considerations. Initial frequentist power calculations using conservative event rates from post hospital extended duration VTE trials in medically ill patients selected for increased risk suggest that roughly 7000 patients will be required to show the superiority of apixaban to placebo, and the superiority of apixaban to aspirin. These numbers will be used for initial overarching

planning; however, to accommodate an adaptive design, sample size will not be pre-determined for any particular Stage after Stage 1 so that “in-flight” changes can be made. There will be interim monitoring to allow early stopping for futility, efficacy, or safety.

6.4 Strategies for recruitment and retention

The study investigators will adapt to the evolving landscape of the pandemic by leveraging the networks of networks already established within NIH including all 50 states and possible international locations. It is anticipated that there will be differences in timing of areas of the United States and the world that become hot-spots for COVID-19 illness over time, based on propagation patterns, local social distancing rules and compliance with those rules. Through the use of simple on-line and easily adapted EDC systems, sites will be activated when the local rate of new COVID-19 cases exceeds a threshold beyond which recruitment is feasible, and will place other sites on hold as needed when disease activity wanes in their geographic areas.

Screening and enrollment will occur in emergency departments or other appropriate outpatient urgent care settings or by review of positive test results from all types of testing facilities. Screening of symptomatic patients will be performed by on-site or remote study staff for trial exclusion and inclusion criteria. Sites or remote study staff must be able to confirm SARS-CoV-2 test results within the past 14 days and have the ability to arrange for CBC, creatinine, D-dimer, and CRP tests prior to starting study drug treatment. Sites must have the ability to enroll minority participants who may preferentially use emergency department, other urgent care health facilities, or free standing testing facilities.

7 Study Assessments and Procedures

Error! Reference source not found. presents the flow chart/time and assessment schedule

Procedure	Screen:	Baseline:	Randomize	Post randomize before starting drug	Treatment initiation *	Confirm all lab test results entered in EDC	Weekly follow up	End of Treatment	End of Safety Period
Timeline	**Day 14 through Day 0**		**Day 0**		**Day 1**		**Day 7, 14, 21, 28, 35**	**Day 45**	**Day 75**
A. ED, URGENT CARE FACILITY									
Medical history	X	X							
Assess inclusion/exclusion		X							
SARS-Cov-2 result or in process		X							
Informed consent		X							
Randomize			X						
Laboratory tests 1		X				X			
Platelet count result or in process		X							
Calculated Cr/cl result or in process		X							
hsCRP result or in process		X							
D-dimer result or in process		X							
Pregnancy test result: must be known before starting drug		X							
B. FREESTANDING TEST CENTER									
Medical history	X	X							
Assess inclusion/ exclusion		X							
SARS-CoV-2 result	X								
Informed consent			X						
Randomize			X						
Laboratory tests 1				X		X			
Platelet count result or in process				X					
Calculated Cr/cl result or in process				X					
hsCRP result or in process				X					
D-dimer result or in process				X					
Pregnancy test results must be known before starting drug 2				X					
ALL									
Drug receipt				X					
Start study drug					X				
Assess adherence/compliance							X	X	
Event assessment					X		X	X	X

*Day 1 is defined as date of starting treatment. The interval between day 0 and day 1 can be more than 1 calendar day

1. Study drug will be stopped if lab values outside acceptable values per protocol section XX

2. Urine or serum hCG test for pregnancy results be known before participant starts study treatment

7.1Study assessments

Laboratory tests:

Patients will only be randomized after confirmation of SARS-Co-V2 positive results.

To allow for different enrollment pathways, laboratory tests can be done at different time points, either before or after randomization but prior to starting study treatment. Serum or urine pregnancy test results for WOCBP must be available prior to starting study treatment. Participants with platelet and creatinine test results not meeting eligibility criteria will be told to discontinue study medication if already started.

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Post initiation of study medication assessments: Visits following informed consent in which SARS-CoV-2 testing and baseline labs are performed may be conducted using virtual technology and /or direct telephone contact. If electronic technology is used, contact will be escalated to direct telephone contact in any case where an unexpected problem occurs, a safety issue is reported, an endpoint is indicated, or any other relevant health-related event is reported.

Post-randomization study assessments will include 1) confirmation of drug receipt and drug administration instructions; 2) frequent (every 5-8 days) reporting of treatment adherence, safety issues, endpoint indications, or other relevant health-related events throughout the treatment period; and 3) frequent (every 5-8 days) reporting of safety issues, endpoint indications, or other relevant health-related events throughout the 30-day safety follow up period.

Confirmation of drug receipt, drug administration instructions, reporting of endpoints will be discussed with electronic and verbal confirmation with subjects. Medication adherence information will be collected by telephone or other electronic methods every 5-8

days after initial contact. Follow-up will utilize a combination of telephone calls and electronic mechanisms.

8 Reasons for Withdrawal or Termination of study treatment

8.1 Occurrence of outcome events

Subjects must discontinue treatment if meeting any of the composite endpoints of the primary outcome or safety outcomes as well as for hospitalization for any indication.

- Hospitalization for cardiovascular/pulmonary events
- Symptomatic DVT
- PE
- Arterial thrombotic events including MI, ischemic stroke, arterial thromboembolism
- Fatal event
- Major bleeding
- new indication for therapeutic anticoagulation or antiplatelet therapy

Trial follow-up and data collection extends through the end of the 75 day follow-up regardless of study drug discontinuation.

Contact with subjects will use multiple modalities including email, SMS text, and telephone. Details for the process for managing contact with patients not responding to these methods or those deemed lost to follow will be outlined in the Operations Manual.

8.2 Voluntary Withdrawal

Participants are free to withdraw from participation in the study at any time upon request. Participation in the study will be terminated if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

8.3 Premature Termination or Suspension of Study

All deaths, SAE, and related critical events occurring within the 75 day study period will be reviewed by the DSMB. The decision to stop or suspend the study will be made the DSMB after considering the totality of the data and the benefit-risk of continuing the study and in accordance with the stopping rules defined in the DSMB charter.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension of one arm or all arms of the trial include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in a strategy, such as excess mortality and major bleeding
- Demonstration of efficacy or lack thereof that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and to the satisfaction of satisfy the sponsor, the IRB and the FDA.

9 STUDY AGENTS

9.1 Study Agent Supply

In Stage 1, Bristol Myers Squibb (BMS) will be responsible for provision of study drug and the blinded clinical trial labeling for all drug product including placebos, aspirin, apixaban, for this investigator sponsored trial. BMS quality will perform the appropriate GMP quality release before shipping the product to a central location to the investigator/sponsor. Bulk shipping of drug kits to the Brigham and Women's Hospital, for further distribution to the subjects will be performed per Good Distribution Practices and instructions for good receipt will be listed on the appropriate packing list.

Labelled study treatment packs will be stored at the Brigham and Women's Hospital. Individual participants study treatment, identified by a study randomization number assigned by the secure IWRS system will be shipped overnight using FED-EX from academic research offices at Brigham and Women's hospital in Boston to randomized participants. All study drug will be packaged in child-proof bottles within a tamper resistant box in keeping with a "low-touch" strategy to minimize patient study visits and to avoid unused study drug accruing at inactive sites. Once an eligible trial participant has been identified and provides informed consent, the EDC will generate a randomization code that in turn will allow trained BWH staff to select the correct small box containing treatment for that participant and place it inside of a FedEx container for next day delivery to the participant's home or place of living. The BWH staff will use the FedEx tracking software along with electronic and where needed telephone contact to ensure receipt of drug by the trial participant. Re-shipping may be done is participants confirm that the study drug is lost.

Follow up to ensure receipt of assigned study medication or placebo and review of administration instructions will be performed by either electronic or telephone contact within 24 hours of patient receipt of the shipment. Trained study staff will be available for any problems

with drug delivery or drug questions. In any subsequent stages, alternative sourcing for novel agents and matching placebo will be required.

For simplicity and to increase adherence and compliance, each participant will receive two pill bottles, one labeled “Bottle A-AM” and one labeled “Bottle B-PM”. Each bottle will contain 45 tablets adequate for the duration of the trial. All drug will be overnight shipped to the participants home in the USA to avoid the need for hospital pharmacy interventions and to ensure that drug supply is distributed efficiently is a disease setting that is likely to undergo geographic change over time.

For those allocated to active apixaban 2.5 mg po bid, both the AM and PM bottle will contain active apixaban 2.5mg tablets.

For those allocated to active apixaban 5.0 mg po bid, both the AM and PM bottle will contain active apixaban 5.0 mg tablets.

For those allocated to active aspirin 81 mg po qd, the AM bottle will contain active aspirin 81 mg and the PM bottle will contain matching aspirin placebo.

Finally, for those allocated to placebo, the AM bottle will contain apixaban placebo and the PM bottle will contain apixaban placebo.

By so doing, all patients will be taking two daily pills that look and feel identical to each other.

9.2 Indications for stopping assigned treatment

The study team will instruct patients to stop study medications when any of the following occur:

- Any hospitalization
- Primary endpoint
- New indication for prophylactic or therapeutic anticoagulation
- New indication for antiplatelet therapy

9.3 Interruption of study treatment.

9.3.1 Outpatient bleeding

If participant experiences a bleeding event, the patient will be instructed to stop the study drug. The participant will be instructed to contact the call center for instructions on appropriateness and timing of restarting therapy. Patients will be given written and video instructions (video 2) for when to call for minor symptoms of bleeding including any bleeding that takes more than 10 minutes to stop, bleeding gums, bruising more than usual, a period that is heavier than usual, or nosebleeds.

9.3.2 Need for unblinding

When knowledge of the subject's randomized treatment assignment would have a meaningful impact on individual management, for example in cases of clinically significant bleeding or the need for urgent invasive procedures, the subject's treatment assignment should be stopped and unblinded which will be performed by BWH emergency care ACTIV-IV outpatient research assistants with 24/7 accessibility with access to EDC and with physician back up and support. This information will be provided to those who are caring for the subject and as few other people

as possible. In these cases, we will minimize bias by assuring that the clinical events committee remains blinded to treatment assignment, even if the treating clinician has been unblinded.

Every subject will be provided with an emergency care card in the study medications package. The will be instructed to bring this to any healthcare provider when they need to seek medical care. They will also be provided with a rubber bracelet with an emergency contact number that can be called in case of need for emergency car and/or unblinding of treatment. The alert card will:

- indicate that the subject is participating in a double-blind clinical trial
- note that the subject may be receiving either apixaban, aspirin, or placebo
- include the contact number to contact responsible trial staff to provide information to emergency medical personnel with unblinding information

10 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. All reported non-serious AE will be collected and handled as described in Appendix F.

SERIOUS ADVERSE EVENTS

A ***Serious 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
- 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 [eg, 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 (eg, 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, these events must be reported within the SAE reporting timeline.

Details of the adverse event collection and reporting process can be found in Appendix F.

Participants will be queried at each study contact for new encounters with healthcare providers including hospital visits or hospitalizations, and for unusual health conditions for which they have not sought medical assistance. Participants who respond with new symptoms or who have

seen a healthcare provider since last assessment will be called by the study Call Center. Procedures for responding to these calls and collecting pertinent medical records will be outlined in the Operations Manual.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical and Analytical Plans (SAP)

A formal statistical analysis plan (SAP) will be created prior to the completion of the study and before database lock. The SAP will include additional details about the statistical analyses, including analysis of specified populations, plans for addressing missing data, and planned sensitivity analyses. The pre-specified SAP will also address stratification of efficacy and safety according to baseline levels of both D-dimer and CRP.

11.2 Power and Sample Size Calculations

The primary efficacy analysis will be the comparison of frequency of the composite of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days among the four study groups using a modified ITT approach. The primary safety analysis will be the comparison of ISTH major bleeding at 45 days between the four study groups. Additional safety analyses will be conducted after an additional 30-day safety follow-up period and will include the full 75 days of follow-up. Subgroup analyses will focus on the evaluation of individual outcome events in each treatment arm within groups defined by baseline D-dimer, hsCRP, and prespecified patient-level factors.

In a retrospective sub-analysis of the Magellan trial which evaluated an enriched population of high-risk cohort of medically-ill patients that included D-dimer level greater than 2 x ULN which approximates the risk we expect in our COVID-19 cohort,[20] the outcome event rate was 5.1% in the apixaban group and 7.9% in the placebo group. We therefore considered control group primary outcome event rates ranging from 6% to 12% and assumed a one-sided superiority test

for comparing the proportion of patients with an event in an active arm as compared to the control arm using a simple chi-square statistic with alpha=0.025. We determined the samples sizes required to provide 80% and 90% power to detect a relative reduction of 33% in the 45-day primary outcome event rates between two assigned treatment groups shown in the **Table** below. Based on these estimates, we propose to enroll a total sample of N=7000 patients with N=1750 patients assigned to each of the four treatment arms. Assuming a placebo event rate of 8.0%, a trial with N=1750 patients in each arm will have 80% power to detect superiority of apixaban 5.0 mg to placebo when there is a 30% relative reduction in risk (i.e. 8.0% vs. 5.62%) and 90% power with a 34% relative reduction (i.e. 8.0% vs. 5.28%). Assuming an event rate of 6.0% with aspirin, a trial with N=1750 patients in each arm will have 80% power to detect superiority of apixaban 5.0 mg to aspirin when there is a 34% relative reduction in risk (i.e. 6.0% vs. 3.94%) and 90% power with a 39% relative reduction (i.e. 6.0% vs. 3.65%). These event rates are plausible based on the current literature. This pragmatic randomized clinical trial has excellent power to detect clinically meaningful differences between the treatment arms with respect to the 45-day composite outcome on both the absolute and the relative scales. This trial will have limited power to detect small differences in the outcome rate.

Table 11-1 - Estimated total sample size in 4 arms required to test one treatment group against control group with a one-sided superiority test and alpha=0.025.

Control Group Event Rate	Treatment Group Event Rate	Risk Ratio	Risk Difference	Total Sample Size for 80% Power	Total Sample Size for 90% Power
12.0%	8.0%	0.667	4.0%	3520	4708
10.0%	6.67%	0.667	3.33%	4312	5772
8.0%	5.33%	0.667	2.67%	5464	7316
6.0%	4.0%	0.667	2.0%	7444	9964

11.3 Primary Outcome Analysis

The modified ITT principle will be used for the primary treatment comparisons of trial outcomes such that only subjects who initiate treatment and have at least one follow-up visit**.** A follow-up visit includes a contact where patient-reported outcomes or site-reported outcomes about patient status are collected. will be included in the analysis, and trial follow up will begin at the time of treatment initiation. For Stage 1, the primary endpoint, the composite of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment in the four treatment groups, will be modeled using a logistic regression model with treatment assignment as the independent variable and adjusting for trial stratification variables (i.e., country), and baseline risk factors including age, sex, race/ethnicity, D-dimer, and hsCRP, weight and calculated creatinine clearance. If the number of mITT patients with a primary endpoint event is low (<50 patients), a logistic regression model adjusting only for the trial stratification variables will be used as the primary model to assess the effect of assigned treatment. The placebo arm will serve as the "reference group" in this model, and the primary outcome analysis will involve testing whether the coefficient for each active treatment group relative to the reference placebo group is equal to 0. For each of the designated treatment comparisons, a one-sided test for superiority will be used such that the type 1 error rate will be set to alpha=0.025. Other pairwise treatment

comparisons will be conducted, and in addition, the effects of treatment of the combined prophylactic and therapeutic doses of apixaban will be compared with placebo.

Unadjusted event rates for each treatment group, and pairwise relative risks and the absolute risk differences with 95% confidence intervals will be calculated and presented.

If clinically meaningful imbalances in baseline risk factors are detected between two randomized treatment groups, multivariable logistic regression will be used to adjust for these factors as a sensitivity analysis.

11.4 Secondary Outcome Analyses

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 45-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 pairwise relative risks and the absolute risk difference between treatment groups will be calculated with their 95% confidence intervals for each of the defined secondary endpoints. In addition to the above, the effects of treatment in the outpatient setting of the combined prophylactic and therapeutic doses of apixaban will be compared with placebo.

Kaplan-Meier cumulative incidence curves will be created for the primary composite endpoint up to 45 days after treatment initiation, and log-rank statistics will be computed to compare the time to event data among treatment groups. The 95% confidence interval for the estimated cumulative event rate at 45 days will be determined for each treatment group. Pairwise differences and 95% confidence intervals for differences will be computed. The combined prophylactic and therapeutic doses of apixaban will be compared with placebo.

Kruskal-Wallace tests will be used to compare the distribution of the clinical rank-based score (scores range from 1-9 with lower scores indicating better outcomes) among the assigned treatment groups. Pairwise comparisons will be conducted to determine if one treatment has a "better" outcome relative to another.

11.5 Sub-group Analyses and Effect Modification

A select number of subgroup analyses will be performed based on pre-specified baseline factors that potentially modify the effect of treatment. These will include D-dimer , hsCRP , age (<60 years, ≥60 years), sex, race/ethnicity (white non-Hispanic, Black non-Hispanic, Hispanic, other), and country. The rate of the 45-day primary composite outcome and the safety outcomes will be compared by assigned treatment within pre-defined subgroups. We will assess whether there is evidence that each subgroup variable modifies treatment effectiveness by creating a logistic regression model including the subgroup variable, treatment assignment, and the interaction between the subgroup variable and treatment assignment and evaluating the significance of the interaction term. Models that evaluate whether continuous variables (d-dimer, CRP and age) modify the assigned treatment effect on the primary endpoint will also be created.

11.6 Safety Analyses

We will compare the rate of ISTH major bleeding and the rate of ISTH clinically relevant non-major bleeding (CRNMB)[28] during the 45-day treatment period and during the additional 30 day safety follow up period between the groups assigned to apixaban 5.0 mg and apixaban 2.5 mg relative to aspirin and relative to placebo alone. DIC will also be assessed at 45 days. 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 95% confidence intervals will be calculated. Analyses of the bleeding outcomes that occur during the

full 75-day follow-up period (i.e. 45 day treatment period plus the 30 day safety follow-up) will also be conducted as part of the trial safety analyses.

11.7 Adherence and Retention Analyses

Receipt of planned therapy will be recorded on electronic case report forms. The proportion of patients evaluated with less than 45-days of follow-up (the primary outcome assessment time) will be tabulated. Every effort will be made to recontact patients who are unreachable. Due to the short timeline of trial participation we anticipate 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.

11.8 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 and transformations will be applied as needed. All variables will be summarized using mean, median, standard deviation, and range (for continuous variables) and frequency (for categorical variables). Baseline characteristics will be examined with respect to assigned treatment group to verify randomization balance.

11.9 Planned Interim Analysis

An independent data safety and monitoring board (DSMB) will review all interim analyses prepared by an unblinded statistician. These analyses will be critical for driving that adaptive changes made based on in-trial accrued data. Eligibility criteria, efficacy, and safety endpoints will be analyzed based 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. Please see Appendix H for full details of the efficacy, futility, and safety monitoring plan for DSMB review.

A Bayesian analytic approach is proposed for the interim monitoring plan in order to utilize prior information when estimating the posterior probabilities in the sequential interim analyses. The study team will work with the DSMB to define timing of the interim analyses and decisions rules to test the relative effectiveness of each active treatment group as compared to the control group with respect to the primary outcome based on the accruing data from appropriate randomized patients. Initially, the placebo group will serve as the “control group”; however, if the placebo arm is dropped and the trial continues, another treatment arm will be designated as the control group for future treatment comparisons

Decision rules will be established for efficacy based on the posterior probability that the active treatment regimen is beneficial as compared to placebo with respect to the primary endpoint. Assuming a non-informative prior distribution for each odds ratio at the first interim analysis, we will calculate the posterior probability that an active treatment is superior to placebo. We will update these posterior probabilities with new data at each subsequent interim analysis. If the posterior probability exceeds the pre-specified threshold for superiority at any of the interim analyses, the superior treatment will be declared efficacious and the other treatment may be dropped. Prior to initiation of the first interim analysis, simulation studies will be conducted to define the precise decision rules such that the resulting estimated type 1 error over the expected number of looks approximates a one-sided alpha=0.025. See Appendix H for more details.

Decision rules will also be developed for assessing futility of the active treatments based on simulation studies. That is, the posterior probability that each of the active treatments is inferior or equivalent to placebo with respect to the primary endpoint will be calculated assuming non-informative priors at the outset of the trial. When the posterior probability exceeds a specified threshold, futility will be established and the respective active therapy may be dropped from the trial. See Appendix H for more details.

11.10 Safety Review

We will monitor the rate of ISTH major bleeding and the rate of ISTH clinically relevant non-major bleeding (CRNMB) [28] from accruing data on a regular and predetermined basis. We anticipate that the rate of major bleeding will be very low. If there is evidence of excess bleeding in the active arms, a new composite outcome including all of the events in the primary efficacy outcome and the safety bleeding events will be considered and analyzed.

11.11 Analyses Stratified by Baseline Levels of D-dimer and CRP

Beyond its primary aim, a major interest of the trial is to address the net benefit-to-risk ratio for oral anticoagulation and oral antithrombotic therapy as compared to placebo across increasing thresholds of D-dimer and across increasing thresholds of hsCRP. These analyses will be pre-specified and are part of the overall trial design; should either net benefit or net risk relate to baseline levels of D-dimer or hsCRP, the DSMB may suggest that different eligibility thresholds be used for these biomarkers going forward.

The study will assess the overall event rate for the primary endpoint and the safety endpoint, irrespective of assigned treatment group, by varying levels of D-dimer and CRP. The study investigators, together with the DSMB, will make inferences based on these analyses of event rates by biomarker level (without incorporating treatment assignment). The DSMB could recommend that subgroups of low risk patients be excluded from the trial based on very low observed primary endpoint event rates in the identified groups.

The DSMB will also evaluate the rates of the primary endpoint, secondary endpoints and the safety endpoints by assigned treatment groups within pre-specified subgroups defined by D-dimer level and CRP level.

11.12 Analyses of Duration of Treatment

The optimal length of treatment is not well-understood in this clinical setting. Hence, we will examine the timing of clinical thrombotic events and safety hemorrhagic events based on the accruing data. Kaplan-Meier cumulative incidence 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. If there is a strong indication that benefits of a given treatment occur early and adverse events occur late in the 45 day treatment period, the DSMB may recommend that the relevant treatment arms be stopped and replaced by treatment arms where the duration of therapy is shortened to 21 days.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be assessed by the Coordinating Center and documentation required for clarification/resolution will be obtained.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

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

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent forms 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 forms will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent 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 documentation of informed consent is required prior to starting study treatments.

Different pathways for identifyingscreen-eligible patients are described in section 5. Based on the different approaches, in person or remote e-consent can be obtained. A copy will Participants can consent to several trial components including the intervention trial, the biobank, and/or if ultimately not eligible for the intervention trial or declines to participate, the patient registry. For potential participants who have had previous positive SARS-CoV-2 test results, site study personnel can contact the potential participant to discuss the trial by telephone, and if participant is interested, arrange to obtain creatinine clearance, platelet count, D-dimer, CRP,

screen for eligibility, and will follow consent and randomization procedures as in section 5, with a copy of the consent form provided to the participant. t.

Consent for participating in the biobank sample collection and/or the registry will be as described in section 5.1

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained following institutional COVID policy to protect study staff. Subjects will be given information regarding participation in the trial using a combination of in-person and video technology to describe the trial in layman's terms to the patient.

Additional consent for biobanking at sites participating in a biobank component can be obtained with this consent form. Consent for participation in the registry study will also be obtained at this time for patients who test positive for SARS-CoV-2 but do not meet eligibility criteria or decline to participate in treatment.

As part of all consent forms, patients will give consent to provide all necessary and available contact information to allow contact by telephone, SMS text, email, or other similar electronic forms of communication.

Patients will have the ability to ask any questions that may arise with answers provided by both onsite staff, call center staff, and by electronic formats. 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 family or friends or think about it

prior to agreeing to participate. 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 either with paper copy or electronically. 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.

13.4 Posting of Clinical Trial Consent Form

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

13.5 Participant and Data Confidentiality

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, 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 direct to participant shipment of study drug and for 75 day 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 included in the patient registry or 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 University of Pittsburgh Data Coordinating Center.

14 Data Handling and Record Keeping

14.1 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.

14.2 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.

14.3 Protocol Deviations

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

It is the responsibility of the Coordinating Center to use continuous vigilance to identify and report deviations.

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

14.4 Publication and Data Sharing Policy

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.

15 Study Finances

15.1 Funding Source

NHLBI ACTIV-IV

15.2 Costs to the Participant

Participant health insurance may be billed for the costs of medical care during this study since these expenses would have happened even if you were not in the study, if their insurance does not cover these costs or participants do not have insurance, these costs will be participant responsibility.

16 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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18 Appendix A: Definition and Determination of Outcomes

18.1 Outcome definitions

Hospitalization for cardiovascular/pulmonary events due to COVID-19
Any hospitalization for cardiovascular/pulmonary events due toCOVID-19 due to cardiac events including ACS, MI, arterial thromboembolism, ischemic stroke, pulmonary events including hypoxemia, hypoxemic respiratory failure, ARDS, VTE, or hemorrhagic events as defined in greater detail bel0w.

Deep venous thrombosis
Deep venous thrombosis will be diagnosed by formal venous ultrasound or point-of-care ultrasound (POCUS) performed by provider and documented in a note.

Pulmonary embolism

Pulmonary embolism will be confirmed by chest CT with PE protocol or pulmonary angiography, or deemed “highly-likely” by provider as evidenced by, for example, “clot in transit” on echocardiogram or acute hemodynamic instability with acute right-ventricular dysfunction, for which a clinician believes systemic anticoagulation and/or fibrinolytic is indicated.

Presumed venous thromboembolism

COVID-19 has presented many clinical challenges including difficulty with obtaining diagnostic imaging due to logistical issues such as patient travel when travel may be restricted at the local level or due to concern for spread of COVID-19 to imaging personnel. The category of presumed PE may be diagnosed when a patient presents with clinical signs and symptoms of PE, not limited to dyspnea, cough, hypoxemia, tachycardia, appropriate EKG changes, or evidence of right heart strain on echocardiogram, when chest CT or pulmonary angiography are unable to be performed and therapeutic dose anticoagulation is prescribed by a physician. Presumed deep vein thrombosis diagnosis may be made when a patient presents with a swollen, painful, or discolored extremity, and the treating physician decides to initiate therapeutic dose anticoagulation without obtaining imaging.

Ischemic stroke/Arterial thromboembolism

Ischemic stroke or systemic embolism as diagnosed by imaging (i.e.: head CT, extremity CT angiogram) or deemed “highly-likely” by provider based on physical examination (i.e., acute hemiplegia thought to be due to ischemic stroke, acute extremity hypoperfusion).

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 99% with ECG changes consistent with ischemia plus: new/ presumed new wall-motion abnormalities or other imaging evidence of MI; potentially ischemic symptoms; and abnormal coronary angiography. This diagnosis is made locally.

ISTH Defined Major Bleeding

Bleeding that:

1. Resulted in death,
2. Occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), including hemorrhagic stroke and intracranial hemorrhage, or
3. Associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells

Clinically Relevant Non-Major Bleeding

Bleeding that resulted in hospitalization, medical or surgical intervention for bleeding, an unscheduled clinic visit, or a change in physician-directed antithrombotic therapy.

Fatal Events

Any death occurring during outpatient treatment or during hospitalization.

19 APPENDIX B Strong inducers/inhibitors of P-GP and CYP3A4

See also https://covid19-druginteractions.org/ for possible new COVID-19 treatments and apixaban

Strong inhibitors of both CYP3A4 and P-GP:

- atazanavir
- boceprevir
-
- conivaptan
- darunavir
- darunavir/ritonavir
-
- indinavir
- indinavir/ritonavir
- itraconazole
- ketoconazole
- lopinavir/ritonavir
- nelfinavir
- nefazodone
- posaconazole
- ritonavir
- saquinavir
- telaprevir
- telithromycin

- voriconazole

Strong inducers of both CYP3A4 and P-GP:

- avasimibe
- carbamazepine
- fosphenytoin
- phenytoin
- phenobarbital
- primidone
- rifampicin
- St John’s wort

20 APPENDIX C: Requirements for Sites

Participants can be identified either in emergency departments or in appropriate healthcare facilities capable of performing all required assessments and perform or confirm COVID-19 test results. In addition to emergency department settings, these can include COVID-19 testing sites within hospitals such as adjacent tents, urgent care centers, and similar medical care facilities that have the ability to obtain CBC, creatinine, D-dimer, and CRP data at the time of COVID-19 testing or with verification of positive SARS-CoV-2 PCR or antigen test within the past 14 days, pathway 5.1.1 A. Free standing test sites that identify positive patients can refer to central study staff of the research call center who will be able to determine eligibility based on criteria as described in section 6, Study Population, screen for the inclusion and exclusion criteria of the trial, and perform assessments and laboratory values described in section 7, see pathway 5.1.1 B below. Hybrid models using a combination of steps for SARS-COV-2 testing, lab draws, consent and randomization from both ED/urgent care and freestanding test center pathways can be used as in 5.1.1 C. All participants must be able to have blood drawn for CBC, creatinine, D-dimer, and hsCRP; this can be performed by home health clinician visits or clinical facility and does not have to have been performed at the time of the initial SARS-CoV-2 test. Test results do not have to be resulted prior to randomization but laboratory tests must be drawn prior to starting study treatment. Serum or urine pregnancy test results in WOCBP need to be known prior to starting study treatment.

21 Appendix D: Consent forms

See attached

22 Appendix E: definitions of covid-19 symptoms

CDC list of symptoms associated with COVID-19 link to website:

https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

23 Appendix F: ADVERSE EVENT Collection and REPORTING INFORMATION

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) will be provided to BMS in aggregate via final study reports a specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information will also be collected following the subject's written consent to participate in the study.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information will begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) will be collected continuously during the 45 day treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

SERIOUS ADVERSE EVENT

The DCC/Medical Monitor must report study endpoints that are serious adverse events in accordance with the protocol (21 CFR 312.64(b)). Because endpoints are specifically defined in the protocol and collected on study case report forms, it is not required that they be submitted on the serious adverse event case report form. The exception to this adverse events reporting

requirement is when there is evidence suggesting a causal relationship between a drug and an event (e.g., death from anaphylaxis). In this case, the DCC/Medical Monitor must immediately report the event to the sponsor, even if the event is a component of the endpoint (e.g., all-cause mortality) (21 CFR 312.64(b)). “Safety endpoints,” as described in section V.A.3.a, are not considered “study endpoints” and, therefore, must be reported to the sponsor immediately (21 CFR 312.64(b)).

- All Serious Adverse Events (SAEs) that occur following the subject’s written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The DCC/Medical Monitor 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 DCC/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 SAE Report Form.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- ✓ The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- ✓ The MedWatch form is available at: MedWatch 3500 Form

- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
    - The DCC/Medical Monitor 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 DCC/Medical Monitor 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 the DCC/Medical Monitor 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 DCC/Medical Monitor 's responsibility to report events to their local 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 DCC/Medical Monitor 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 DCC/Medical Monitor 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 subjects, clinically significant safety finding from a nonclinical (eg, 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 DCC/Medical Monitor 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 DCC/Medical Monitor and IRB/IEC will determine if the informed consent requires revision. The DCC/Medical Monitor should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same DCC/Medical Monitor 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 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). 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 subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

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 (eg, 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 (eg, dose tapering if necessary for participant).

The DCC/Medical Monitor must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

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 CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

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.

24 Appendix G: **Call Center Structure**

Located at the University of Illinois at Chicago (UIC), the ACTIV-4 Call Center is a unit within the Population Health Sciences Program.

The Call center will employ the Five9 telephony system. The Call Center will record all telephone calls, and store this information in HIPAA-compliant folders at UIC for training and QC activities. The recorded calls will serve as "source documents" for Call Center activities, and will be available to authorized study personnel collaborating in the ACTIV-4 network of networks. The Call Center is staffed by bi-lingual (English and Spanish) and bicultural agents. Additional Call Center agents can be added to meet the needs of the ACTIV-4 studies (other languages, time zones, other countries). Call center agents do not need to be co-located, which is an advantage during COVID-19 pandemic precautions, and provides the Call Center an opportunity to scale its operations to support multiple studies. Training for additional Call Center agents will be provided by UIC, including agents who are employees at other universities. Call Center agents will access the eSOCDAT electronic data capture (EDC) system for data entry.

25 Appendix H: **Monitoring plan for efficacy, futility and safety in the Outpatient Trial for DSMB review**

1. Monitoring of Effectiveness Outcomes

The primary aim of the COVID-19 Outpatient trial is to compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) anticoagulation at prophylactic doses; with (ii) anticoagulation at therapeutic doses; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on the primary composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment among the study population of non-hospitalized COVID-19 patients aged $\geq$ 40 years.

The trial primary, secondary and safety outcomes are listed below.

Primary outcome: a composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality up to 45 days after initiation of assigned treatment.

Secondary outcomes: (at 45 days):

1. Hospitalization for cardiovascular/pulmonary events
2. Death occurring without antecedent hospitalization
3. Symptomatic DVT
4. Pulmonary embolism
5. Arterial thrombotic events including MI, ischemic stroke, other arterial thromboembolism
6. All-cause mortality
7. Time-to-event for the composite endpoint
8. Clinical rank-based score

Safety outcomes: (at 45 days and at 75 days)

1. Severe bleeding (ISTH major bleeding)
2. Mild bleeding (ISTH CRNMB)
3. Development of DIC

Clinical event rates for the primary, secondary and safety outcomes will be used to monitor potential benefit or harm of treatment strategies for patients with COVID-19. The DSMB will conduct a systematic evaluation of all trial outcomes for the overall trial cohort and stratified by assigned treatment group at established regular intervals.

Sequential interim monitoring of the assigned treatment comparison with formal decision rules will be used for efficacy and futility. Decision rules for efficacy of active drug versus placebo will

be conducted such that the overall type I error is maintained at the pre-specified level of alpha=0.025 for the one-sided test. Formal interim futility analyses will be conducted to assess the likelihood that each of the active treatments is inferior or equivalent to placebo with respect to the primary endpoint. Initially, the placebo group will serve as the "control group"; however, if the placebo arm is dropped and the trial continues, the aspirin treatment arm will be designated as the control group for future treatment comparisons. Safety data will be presented and analyzed at each meeting, but no formal decision rules will be established a priori for safety. Data will be presented so that the DSMB can evaluate the net risk benefit ratio for each treatment. Detailed information about the observed rate of enrollment over time will be presented to the DSMB on a quarterly basis. Using the observed enrollment rates and trends, we will project future sample sizes and estimate the power to detect superiority and/or futility at set intervals.

We estimate that the primary endpoint event rate in the placebo group will be 8%. Since we hypothesize that the active treatments will be beneficial, we estimate that the overall primary endpoint event rate in the trial (i.e. all treatment groups combined) will be this population is approximately 7.0%. We also estimate the overall bleeding event rate will be approximately 1.0%. With a total of N=7000 patients, we therefore assume that we will observe approximately 490 patients with primary endpoint events and 70 with bleeding events.

2. Formal Statistical Interim Monitoring for Efficacy: Superiority

Unadjusted event rates for each treatment group, and pairwise relative risks and the absolute risk differences with 95% confidence intervals will be calculated and presented. In addition, the effects of treatment in the outpatient setting of the combined prophylactic and therapeutic doses of apixaban will be compared with placebo. A logistic regression model will be created for the primary composite endpoint such that the effect of each active treatment group (relative to the placebo reference group) will be estimated adjusting for country, age, sex, race/ethnicity, D-dimer, and hsCRP, weight and calculated creatinine clearance. If the number of mITT patients with a primary endpoint event is low (<50 patients), a logistic regression model adjusting only for the trial stratification variables will be used as the primary model to assess the effect of assigned treatment. The primary analyses for efficacy will be based on the odds ratios,

comparing one treatment to another, derived from this model. One treatment is beneficial compared to another if the [Odds Ratio < 1.00] for the primary composite outcome. Assuming non-informative priors at the first look, we will calculate the posterior probabilities that the [Odds Ratio < 1.00] for each active treatment compared to placebo. If at any analysis time-point, the upper bound of the lower 99% credible interval for the odds ratio is less than 1.00, the active treatment arm will be considered superior.

Thus, the decision rule for superiority is:

- ***Posterior Probability [OR (active vs placebo for the primary endpoint) < 1.00] ≥ 0.99***

Based on preliminary simulations, this threshold corresponds to a type 1 error rate that approximates 0.025 for a one-sided test, accounting for multiple looks. Simulations using a variety of assumptions will be conducted before the first interim look is initiated in order to verify the appropriateness of the proposed superiority threshold for this trial, and modifications to the decision rule may be made based on the simulation results.

The DSMB will use this information to make a recommendation to the NHLBI. The DSMB can recommend that the Outpatient COVID-19 trial should continue as proposed, that one treatment arm may be dropped, that the trial protocol should be modified, or that the Outpatient COVID-19 trial should be terminated early. The final decision to stop trial rests with the NHLBI.

3. Formal Statistical Interim Monitoring for Efficacy: Futility

We will consider dropping an arm of the trial when an active treatment is found to be “no different from” or “inferior to” placebo. Using the same logistic regression model that will be used for the primary analyses for superiority, we will determine the posterior probability that the active arm is equivalent or inferior to placebo. Given that the trial is powered to detect a relative risk reduction of 33% with active treatment, futility will be defined for an active arm if the lower bound of the upper 95% credible interval for the odds ratio comparing the active arm to placebo is greater than 0.75.

Thus, the decision rule for futility is:

- ***Posterior Probability [OR (active vs placebo for the primary endpoint) > 0.75] ≥ 0.95***

This roughly corresponds to the having an estimated Odds Ratio that is 1.00 (or greater) and the two-sided 90% confidence interval extends from 0.75 to 1.33 (or greater).

When the posterior probability exceeds this specified threshold, futility will be established and the respective active therapy may be dropped from the trial. The DSMB will use this information to determine its recommendation to NHLBI, and the NHLBI will make the final decision.

4. Monitoring Safety

Unadjusted event rates for each assigned treatment group, and pairwise relative risks and the absolute risk differences with 95% confidence intervals will be calculated and presented for each of the specified safety outcomes. In addition, a logistic regression model will be created for each safety endpoint such that the effect of each active treatment group (relative to the placebo reference group) will be estimated and the odds ratios, comparing one treatment to another, will be derived from this model. We will not create explicit decision rules based on the bleeding posterior probability.

Prior studies suggest that bleeding safety event rates in this population are likely to be very low (approximately 1.0%). If safety issues arise, the DSMB will use their clinical judgement to assess the potential risks relative to the potential benefits for each active drug compared to control. 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 the monitoring information to determine its recommendation to NHLBI. The DSMB can recommend that the Outpatient COVID-19 trial should continue as proposed, that one treatment arm may be dropped, that the trial protocol should be modified, or that the Outpatient COVID-19 trial should be terminated early for safety reasons.

5. Subgroup Analyses and Effect Modification

A select number of subgroup variables have been specified a priori:

- Quartiles of D-dimer and CRP based on the data
- age (<60 years, ≥60 years)
- sex

- race/ethnicity (white non-Hispanic, Black non-Hispanic, Hispanic, other)
- country, if applicable.

The rate of the primary composite outcome and the rate of the safety outcomes with 95% confidence intervals will be compared by assigned treatment within these pre-defined subgroups. We will assess whether there is evidence that each subgroup variable modifies treatment effectiveness by creating a logistic regression model including the subgroup variable, treatment assignment, and the interaction between the subgroup variable and treatment assignment. The significance of the interaction term will be presented. Additional subgroups may be examined based on data from the trial or information from external sources.

Data will also be presented based on D-dimer and CRP level. In particular, we will examine the distribution of baseline D-dimer and by CRP levels, and we will analyze the overall event rates for the primary endpoint and the safety endpoints, irrespective of assigned treatment group, in each pre-specified subgroup defined by D-dimer and by CRP. If the overall primary endpoint event rates are exceedingly low in the low D-dimer or CRP subgroups, the DSMB may consider adding eligibility criteria to exclude these groups from the trial. Additional analyses will be undertaken to identify appropriate cut-points for defining low and high risk patient subgroups based on D-dimer and CRP levels. These analyses will include the examination of ROC curves from logistic regression models for the primary endpoint (and for safety endpoints) by continuous D-dimer level or CRP level and the examination of LOESS curves for the logit of the primary endpoint (and for the safety endpoint) by continuous D-dimer level or CRP level. The study investigators, together with the DSMB, will make inferences based on these analyses of event rates by biomarker level without incorporating treatment assignment. Only the DSMB is permitted to examine outcomes by assigned treatment group. As noted, the DSMB will evaluate the rates of the primary endpoint, secondary endpoints, and the safety endpoints by assigned treatment groups within pre-specified subgroups defined by D-dimer level and CRP level.

6. Duration of Treatment

Kaplan-Meier cumulative incidence curves will be created to assess the time to the first primary endpoint event and the time to the first safety event, and Nelson-Aalen cumulative hazard

curves will be used to assess the cumulative number of events, irrespective of treatment assignment. Assuming that bleeding events occur at a fairly constant rate over time, we suggest that if ≥ 90% of the primary endpoint events occur in the first 21 days, then the DSMB will consider modifying the treatment arms such that the duration of therapy is shortened to 21 days. Curves stratified by treatment group may be examined before finalizing a recommendation.

ACTIV-IV COVID-19 Outpatient Thrombosis Prevention Trial

Version: 5.7

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