Protocol: ACTIV-4C (Post-Discharge)
COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis

STATISTICAL ANALYSIS PLAN (SAP)

for Stage I Study of Apixaban vs. Placebo

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Thomas L. Ortel, MD, PhD
Professor of Medicine and Pathology
Chief, Division of Hematology
Duke University Medical Center
Durham, NC 27710
Tel. 919-681-6049
Fax. 919-681-6160
E-mail: thomas.ortel@duke.edu

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Study Sponsor:
Thomas L. Ortel, MD, PhD
Professor of Medicine and Pathology
Chief, Division of Hematology
Duke University Medical Center
Durham, NC 27710
Tel. 919-681-6049
Fax. 919-681-6160
E-mail: thomas.ortel@duke.edu

We, the undersigned, have read and approve of this SAP and agree on its content.

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Sponsor Representative and ACTIV4C Protocol Chair – Thomas L. Ortel, MD, PhD

_____
ACTIV-4C Principal Investigator – Tracy Wang, MD MHS MSc

_____
ACTIV-4C Protocol Statistician – Abdus S. Wahed, PhD

_____
ACTIV-4C Protocol Statistician – Kevin J. Anstrom, PhD

_____
ACTIV-4C NHLBI Statistician – Eric Leifer, PhD

_____
ACTIV-4C Protocol Co-Chair – Alison Morris, MD, MS

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LIST OF ABBREVIATIONS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
CRNMB	Clinically Relevant non-Major Bleeding
CE	Composite Endpoint
CEx	Composite Endpoint at Day x
CEATE30	Composite Arterial Endpoint at Day 30
CEVTE30	Composite Venus Endpoint at Day 30
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
DSMB	Data and Safety Monitoring Board
DVT	Deep Venous Thrombosis
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
ICU	Intensive Care Unit
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to Treat
LAR	Legally Authorized Representative
LMWH	Low Molecular Weight Heparin
mITT	Modified ITT
NIH	National Institutes of Health
PE	Pulmonary Embolism
PI	Principal Investigator
QOL&M30	Composite endpoint of EQ5D and Mortality at Day 30
QOL&M90	Composite endpoint of EQ5D and Mortality at Day 90
SAE	Serious Adverse Event
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
VTE	Venous thromboembolism
WHO	World Health Organization

1.0 STUDY AND DOCUMENT OVERVIEW

ACTIV-4C study is an adaptive, prospective, randomized trial designed to compare the effectiveness and safety of antithrombotic therapy with no antithrombotic therapy after hospitalization for 48 hours or longer for Coronavirus disease 2019 (COVID-19) resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For Stage 1 of this study, participants will be randomized to either prophylactic anticoagulation or placebo for 30 days, and then followed for an additional 60 days after the completion of treatment (total duration of follow-up, approximately 90 days).

This document describes the planned statistical analyses that will be conducted during (interim) and at the completion of stage 1 of the study. Once the initial unblinded data review has occurred, only the blinded statistics team members will be allowed to modify the SAP (see **Appendix 1** for the list of blinded and unblinded statisticians). The initial interim review is expected to occur when 20% of the information fraction is accumulated.

The study population corresponds to adults at least 18 years of age with COVID-19 who are hospitalized for 48 hours or longer and who are ready for discharge from the hospital. Patients both with and without intensive care unit (ICU) stay will be included in the study population. Key exclusion criteria are a clinical requirement for anticoagulant therapy (therapeutic dose or prophylactic dose), contraindication to anticoagulant therapy, and anticipated life expectancy < 90 days.

Enrollment into this first stage of the ACTIV-4C study began in February 2021.

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

This first stage of the ACTIV-4C trial uses a group-sequential design where interim analyses are planned to assess the efficacy and futility of the treatments with the potential for early stopping. Proper statistical approaches are used to control type I error at the interim and final analyses. Safety monitoring will be performed throughout the trial and will be periodically reported by the Data and Safety Monitoring Board (DSMB) established for ACTIV-4C which will have oversight responsibility for the study.

2.0 STUDY OBJECTIVES

Primary Objective:

- The primary objective of this first stage of the ACTIV-4C trial is to compare the effects of treatment beginning at the time of discharge from the hospital with either (i) anticoagulation at a prophylactic dose, or (ii) placebo (no anticoagulation) for up to 30 days after randomization on the composite endpoint of venous and arterial thromboembolic outcomes, and all-cause mortality.

Secondary Objectives:

- Secondary Objective 1: To compare the effects of treatment at 30 days after randomization for the composite endpoint of QOL and mortality.
- Secondary Objective 2: To compare the effects of treatment at 90 days after randomization for the composite endpoint of QOL and mortality.
- Secondary Objective 3: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of the composite outcome at 45 days and at 90 days after randomization.
- Secondary Objective 4: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of new, symptomatic VTE (inclusive of Deep Venous Thrombosis (DVT), PE, or other venous thrombosis) for up to 30 days after randomization.
- Secondary Objective 5: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of new, symptomatic ATE (inclusive of ischemic stroke, MI, or peripheral arterial thromboembolism) for up to 30 days after randomization.

Exploratory Objectives:

- Exploratory Objective 1: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of all-cause rehospitalization for up to 90 days after randomization.
- Exploratory Objective 2: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the incidence of all-cause mortality for up to 30 days after randomization.
- Exploratory Objective 3: To compare the effects of treatment beginning at the time of discharge from the hospital with either Arm A or Arm B on the individual domains of EQ5D and the EQ5D visual analog scale for 30 and 90 days after randomization.

3.0 STUDY ENDPOINTS

3.1 PRIMARY STUDY ENDPOINTS

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

3.2 KEY SECONDARY AND EXPLORATORY ENDPOINTS

Key secondary endpoints include the following.

1. The composite endpoint of EQ5D index score and mortality at day 30 following randomization
2. The composite endpoint of EQ5D index score and mortality at day 90 following randomization
3. The composite endpoint for the primary outcome at day 45 following randomization
4. The composite endpoint for the primary outcome at day 90 following randomization
5. Composite endpoint of venous thromboembolic events, including symptomatic DVT of the upper or lower extremities, symptomatic and/or clinically relevant PE, and other symptomatic venous thrombosis, including cerebral sinus and splanchnic vein thrombosis at day 30
6. Composite endpoint of arterial thromboembolic events, including symptomatic ischemic stroke, myocardial infarction, and other symptomatic arterial thromboembolic events at day 30

Secondary endpoints will be formally tested using a fallback approach (see Section 4.3) only if the primary endpoint was statistically significant at the two-sided 5% level.

Exploratory endpoints include the following.

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

Table 1. Summary of important questions of interest and related estimands

Row	Question of Interest	Objective Description / Study Population	Endpoint	Intercurrent Events/Strategy to handle	Population Summary Estimands
1	Does Apixaban reduce the rate of venous and arterial thromboembolic outcomes, and all-cause mortality during 30 days after discharge?	Primary Objective of the Study / All Randomized Participants	Composite endpoint (CE) of venous and arterial thrombotic complications—including new, symptomatic proximal, or distal DVT of the upper or lower extremities, PE, and new thrombosis of other veins (including cerebral sinus and	The only inter-current event will be patient drop-out. The drop-out is expected to be less than 5% and un-related to treatment and their data up to the time of drop-out will be	The difference in the proportion of CE between the Apixaban arm and the placebo arm. A negative value will favor the

			splanchnic veins), ischemic stroke, myocardial infarction, other arterial thromboembolism (e.g., mesenteric or acute limb ischemia), and all-cause mortality by day 30	used in the event determination*	Apixaban arm.
2	Does Apixaban improve the composite of QOL and mortality at 30 days after discharge?	Key Secondary Objective of the Study / All Randomized Participants	Composite endpoint of mortality and EQ5D index at Day 30. All mortality events will be considered worse than any possible EQ5D response [QOL&M30]	The expected rate of missing data for the EQ5D endpoint is expected to be approximately 20%. The odds ratio will be estimated using maximum likelihood methods which yield valid estimators under the MAR (or MCAR) assumptions.	The odds ratio from a proportional odds model with the EQ5D index and mortality endpoint as the response variable. Values greater than 1.0 will favor the Apixaban arm.
3	Does Apixaban improve the composite of QOL and mortality at 90 days after discharge?	Key Secondary Objective of the Study / All Randomized Participants	Composite endpoint of mortality and EQ5D index at Day 90. All mortality events will be considered worse than any possible EQ5D response [QOL&M90]	The expected rate of missing data for the EQ5D endpoint is expected to be approximately 20%. The odds ratio will be estimated using maximum likelihood methods which yield valid estimators under the MAR (or MCAR) assumptions.	The odds ratio from a proportional odds model with the EQ5D index and mortality endpoint as the response variable. Values greater than 1.0 will favor the Apixaban arm.
4	Does Apixaban reduce the rate of venous	Key Secondary Objective of	Composite endpoint of venous thromboembolic	Inter-current events will be death and	The difference in the

	thromboembolic outcomes during 30 days after discharge?	the Study / All Randomized Participants	events, including symptomatic DVT of the upper or lower extremities, symptomatic and/or clinically relevant PE, and other symptomatic venous thrombosis, including cerebral sinus and splanchnic vein thrombosis at day 30 [CEVTE30]	patient drop-out. Patients who died without an intercurrent event will be censored. The drop-out is expected to be less than 5% and un-related to treatment and their data up to the time of drop-out will be used in the event determination*	proportion of CEVTE30 between the Apixaban arm and the placebo arm. A negative value will favor the Apixaban arm.
5	Does Apixaban reduce the rate of arterial thromboembolic outcomes during 30 days after discharge?	Key Secondary Objective of the Study / All Randomized Participants	Composite endpoint of arterial thromboembolic events, including symptomatic ischemic stroke, myocardial infarction, and other symptomatic arterial thromboembolic events at day 30 [CEATE30]	Inter-current events will be death and patient drop-out. Patients who died without an intercurrent event will be censored. The drop-out is expected to be less than 5% and un-related to treatment and a complete-case analysis will be employed*	The difference in the proportion of CEATE30 between the Apixaban arm and the placebo arm. A negative value will favor the Apixaban arm.
6	Does Apixaban reduce the rate of venous and arterial thromboembolic outcomes, and all-cause mortality during 45 days after discharge?	Key Secondary Objective of the Study / All Randomized Participants	Composite endpoint of venous and arterial thrombotic complications—including new, symptomatic proximal, or distal DVT of the upper or lower extremities, PE, and new thrombosis of	The only inter-current event will be patient drop-out. The drop-out is expected to be less than 5% and un-related to treatment and their data up to	The difference in the proportion of CE45 between the Apixaban arm and the placebo arm. A negative

			other veins (including cerebral sinus and splanchnic veins), ischemic stroke, myocardial infarction, other arterial thromboembolism (e.g., mesenteric or acute limb ischemia), and all-cause mortality by day 45 [CE45]	the time of drop-out will be used in the event determination*	value will favor the Apixaban arm.
7	Does Apixaban reduce the rate of venous and arterial thromboembolic outcomes, and all-cause mortality during 90 days after discharge?	Key Secondary Objective of the Study / All Randomized Participants	Composite endpoint of venous and arterial thrombotic complications—including new, symptomatic proximal, or distal DVT of the upper or lower extremities, PE, and new thrombosis of other veins (including cerebral sinus and splanchnic veins), ischemic stroke, myocardial infarction, other arterial thromboembolism (e.g., mesenteric or acute limb ischemia), and all-cause mortality by day 90 [CE90]	The only inter-current event will be patient drop-out. The drop-out is expected to be less than 5% and un-related to treatment and their data up to the time of drop-out will be used in the event determination*	The difference in the proportion of CE90 between the Apixaban arm and the placebo arm. A negative value will favor the Apixaban arm.

*See the sensitivity analysis (Section 4.2)

3.3 SAFETY ENDPOINTS

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

1. Major bleeding
    a. Fatal bleeding
    b. Bleeding into a critical area or organ (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)
    c. Bleeding causing a fall in the hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells
2. Clinically relevant, non-major bleeding
    a. Bleeding requiring medical intervention by a healthcare professional

b. Bleeding leading to hospitalization or an increase in the level of care
c. Bleeding prompting a face-to-face (i.e., not just a telephone or electronic communication) evaluation

3.4 ADJUDICATION OF OUTCOME EVENTS

All patient-reported events will be investigated by the Clinical Coordinating Center, including obtaining information from healthcare facilities where the patient received treatment. An independent, central adjudication committee (ICAC) will review and adjudicate events in a blinded manner without knowledge of treatment allocation. During the study period, the ICAC will adjudicate all suspected occurrences of venous or arterial thromboembolic events, ischemic stroke, acute myocardial infarction, deaths, and re-hospitalization. The ICAC will also review all suspected episodes of bleeding and categorize adjudicated bleeding as major, clinically relevant non-major, or minor bleeding. The Committee will be provided with all relevant documentation related to the events. The criteria and definitions of the study outcomes, as well as the procedures followed by the Committee, will be described in an adjudication manual which will be provided to the ICAC members before the first meeting.

3.5 POWER AND SAMPLE SIZE

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

The MARINER trial reported a 2% event rate for a combined outcome of VTE, MI, CVA, or CV deaths in the placebo group (Spyropoulos, 2018). These rates are expected to be higher in COVID-19 patients who are discharged from the hospital. Recent information from patients discharged alive from the University of Pittsburgh Medical Center suggests that the 30-day mortality rate in this population could be as high as 4%. To be conservative, 4% was used as the expected CE rate of events for the no anticoagulant arm. An effect size of 35% percent risk reduction (risk ratio = 0.65) in the anticoagulant group compared to the no anticoagulant group was used to calculate the expected sample size for the study.

The analysis will use a group-sequential two-sample two-sided Z-test for proportions with pooled standard deviation to test the primary hypothesis at overall significance two-sided level alpha = 0.05. Four equally spaced interim analyses and one final analysis will use O'Brien-Fleming alpha spending boundaries for efficacy and the Hwang-Shih-DeCani boundaries for the futility reviews (O'Brien and Fleming, 1979; Hwang, Shih, and De Cani, 1990). In order to ensure an 80% power to detect a CE rate reduction of 35% through anticoagulation use, the study needs to enroll at least 2,530 participants per arm. Since the primary outcome is observed within 30 days of follow-up, the loss to follow-up and withdrawal of consent rates should be low, and it is estimated that CE will be missing on a maximum of 5% of the participants. Therefore, the sample size required for this study will be approximately 2,660 per

arm. The sample size has been calculated using 2,000 simulations in PASS 13 [PASS 13 Power Analysis and Sample Size bounds Software (2014). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass].

The operating characteristics (type I error and power) of the design has been investigated through simulations under the bounds established in the interim analysis (Section 3.3 below) and under the above assumptions using multiple software packages. The Type I error and Power were both adequate.

3.6 RANDOMIZATION SCHEME

Randomization will be performed for study participants as close to the time of hospital discharge as possible. Hospitalized patients may be screened and approached about the study up to 48 hours before hospital discharge, but final enrollment and randomization should occur as close to the time of discharge as possible. Participants will be randomized in a 1:1 ratio using an online randomization system to either Arm A (apixaban 2.5 mg twice daily), or Arm B (matching placebo). Randomization will be stratified by (1) concomitant use of a single antiplatelet agent (yes/no), and (2) a maximal score of 5 or greater vs. a score of less than 5 by the World Health Organization (WHO) Ordinal Index.

3.7 INTERIM ANALYSES AND DATA MONITORING

3.7.1 INTERIM SAFETY ANALYSES

Safety monitoring will be continuous. In addition to examining the rate of ISTH major bleeding and the rate of ISTH clinically relevant non-major bleeding (CRNMB) in each of the treatment arms, monitoring will include unacceptable toxicity, defined as major bleeding, including hospitalization, and all-cause mortality. Prior studies have shown that the rate of major bleeding will be very low. The degree of evidence about differences in risk of unacceptable toxicity from accruing data will be addressed on a regular and pre-determined basis (e.g. every 3 months or more frequently per DSMB request) and will be shared with the DSMB. Unadjusted safety event rates for each assigned treatment group, and relative risks, and the absolute risk differences with 95% confidence intervals, will be calculated and presented to the DSMB for each of the specified safety outcomes.
Events will be adjudicated centrally by an adjudication committee. The following events will be adjudicated: Hospitalization or Emergency Room/Department visit documented on the related Pharmacist form, DVT, PE or major bleeding is checked as event type, and SAE has hospitalization or prolonged hospitalization as a reason for seriousness.

Appendix 2 provides a list of tables that are presented to DSMB every month.

Full DSMB report every three months, in addition, will contain the listings of all safety events, including the date of onset, relatedness to treatment/unexpectedness, resolution, treatment adjustment, and other detailed narratives. **Appendix 3** provides a list of tables and figures provided to DSMB every 3 months.

Additionally, participants with safety events will be categorized in comparison to those without the safety events using a logistic regression to identify if the safety event was associated with any particular participant characteristics to identify high-risk groups.

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

3.7.2 INTERIM ANALYSES FOR FUTILITY AND EFFICACY REVIEW

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

Assessments of futility will be conducted at all interim looks, whereas efficacy will only be assessed starting at the third interim analysis (after 60% of the information accumulated; **Table 1**). For the efficacy and futility, O'Brien-Fleming analog alpha-spending function and Hwang-Shih-DeCani beta-spending function will be utilized to create the non-binding boundaries. **Table 1** and **Figure 2** provide specific efficacy and futility boundaries at each interim analysis.

Table 1: Stopping Boundaries for Efficacy and Futility based on Z-statistic above.

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

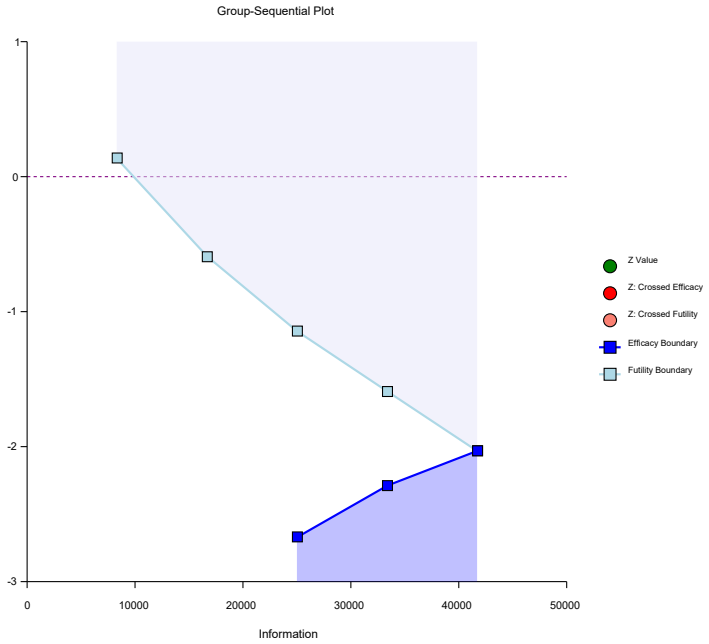

Figure 2: Stopping Boundaries for Efficacy and Futility based on the Z-statistic described above.

3.8 DATA SOURCES

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 at Duke Clinical Research Institute and the University of Illinois-Chicago 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.

Programmed computer edit checks will be run against the database to identify discrepancies and verify the reasonableness of the data. Queries to resolve discrepancies will be generated and resolved by the sites. Analysis datasets will be created by the Data Coordinating Center for the production of tables, figures, and listings. All planned reporting will be based on the analysis datasets, but in the case of emergent safety data, some reporting may occur from the raw eCRF data. All programs written to create analysis datasets and perform analyses will be validated according to Standard Operating Procedures established by the ACTIV4C Data Management and Statistical Analyst teams.

3.9 SOFTWARE PACKAGE

The statistical analyses described in this SAP, as well as the production of tables, listings, and figures, will be performed using SAS®, version 9.4 or higher (SAS Institute, Cary, NC) or R software. Additional statistical software may be used as needed.

3.10 VERIFICATION OF RESULTS

All tables, listings, and graphs will be verified and reviewed before being considered final. The verification process will ensure that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Qualified statisticians or statistical programmers employed at the Data Coordinating Center who have not been previously involved in the production of the original programming will perform the verification procedures. Methods of verification include independent programming, prior to issuance of the draft statistical report, of all analysis datasets and comparison to data listings. Tables, listings, and figures will be reviewed for accuracy, consistency with this analysis plan, consistency within tables/listings/figures, and consistency with the corresponding output. Once verification is complete, all documentation of the verification process will be saved.

3.11 SUBJECT DISPOSITION

The disposition of subjects (number randomized, number who received any amount of the randomly assigned treatment, number completing study drug administration, number who withdrew consent or discontinued from study drug early, and number lost to follow-up, and number who completed the trial) will be summarized by treatment group. The number of subjects screened for inclusion and a breakdown of reasons for exclusion will be summarized. The timing and reasons for early discontinuation of study drug and/or withdrawal from the study will be summarized by treatment group. For the calculation of percentages, subjects who die will not be included in the denominators for visits/assessments beyond their death. Treatment compliance (e.g., number of subjects with missed doses) will be summarized by treatment group. A subject listing of analysis population eligibilities will be generated. A listing of all subjects discontinued from the study after enrollment, broken down by site and treatment group will be provided. The listing will include the reason for discontinuation, treatment group, duration of treatment, and whether or not the blind was broken. Also, for subjects who discontinued from the study after enrollment, a listing of adverse events will be provided. Subject-specific protocol deviations will be summarized by the reason for the deviation, the deviation category, treatment group, disease severity, and (separately) site for all subjects. All subject-specific protocol deviations and non-subject-specific protocol deviations will be included in listings.

3.12 POPULATIONS FOR ANALYSES

The primary analysis will be based on an intention-to-treat (ITT) population, including all participants randomized. Secondary analyses will be based on a modified intention-to-treat (MITT) population consisting of all participants who received at least one dose of the study medications.

4.0 STATISTICAL ANALYSES

4.1 DESCRIPTIVE STATISTICS

Baseline characteristics representing demographic, clinical history, symptom, and biomarker variables will be summarized by treatment arms. The distribution of each variable will be examined. All variables will be summarized using appropriate central tendency (mean/median) and spread measures (standard deviation, 25th and 75th percentiles, or range) for continuous variables and frequency and percent for categorical variables.

4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

As a primary approach, the primary endpoint CE30 will be compared between two arms using a two-sample Z-statistic for proportion (standardized difference between proportion having CE in the anticoagulant arm and matching placebo arm, positive difference favoring anticoagulant arm). More explicitly, denoting p, $p_A$and p_P the estimated proportion of CE30 in the whole sample, anticoagulant and placebo group respectively, the null hypothesis of no difference in the proportions will be tested using the test statistic

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

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

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

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

The CE30 rates will also be modeled using a log-binomial regression model with treatment arm as the independent variable and adjusting for trial stratification variables (i.e., antiplatelet use; WHO ordinal scale score). Secondary analyses of this endpoint will include adjustment for D-dimer levels, intensive care unit stay, patient characteristics, and demographic factors, including race and ethnicity. The matching placebo arm will serve as the “reference group” in this model, and analysis will involve testing whether the coefficient for each active treatment group relative to the reference group is equal to 0, or equivalently, whether the adjusted relative risk for the anti-coagulant arm is equal to 1. The adjusted relative risk and the related confidence interval will be provided.

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

Patients dropping out of the study prior to day 30 will contribute data up to the time of drop-out.

- Sensitivity Analyses

  The primary analysis will be repeated in the MITT analysis population where subjects who did not start the medication will be excluded. For all supplemental and sensitivity analyses, p-values will be

reported and 95% confidence levels will be used for confidence interval estimates. The tabular and graphical summaries described in the previous section will be replicated for the MITT analysis.

The primary analysis will also be repeated using the other subgroups defined in Section 4.6. Each subgroup will be considered separately, and the tabular and graphical summaries described in the previous section will be replicated for each subgroup. In addition, a forest plot will be generated to display the overall treatment difference estimate and CI from each of the within-stratum analyses. These analyses will be performed in the ITT and MITT populations.

The primary analysis uses information from participants who dropped out up to the time of the drop-out. A tipping points sensitivity analysis that systematically and comprehensively varies assumptions about the missing outcomes on the two treatment arms will be applied. These analyses will be two-dimensional and will allow assumptions about the missing outcomes on the two arms to vary independently. These scenarios will include those where dropouts on drug tend to have worse outcomes than dropouts on control. The goal is to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of efficacy.

Further supplementary analyses of the primary endpoint will include the use of Fisher's exact test, Cochran-Mantel-Haenszel test adjusting for stratification factors. Furthermore, a random intercept log-binomial regression of the primary outcome with baseline characteristics including stratification factors and a random intercept for the recruitment site will be performed to assess factors associated with the primary outcome.

To understand the time course of the primary event CE, we will use Kaplan-Meier curves to estimate the cumulative proportion of events over time. Differences between such proportions over time by treatment groups will be assessed using log-rank test adjusting for stratification factors and will further be investigated using Cox proportional hazard models. In addition to the stratification factors, the Cox model will assess other baseline patient characteristics.

4.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT(S)

Six secondary outcomes are of interest in this trial. We will use a fallback method to control for type I error (see page 30 of the Food and Drug Administration guidance on multiple endpoints in clinical trials; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry). More specifically, these secondary outcomes will only be formally tested if the primary hypothesis was rejected at level alpha=0.05. If the study stops without the CE30 test statistic crossing the 'efficacy boundary' or 'futility boundary' (i.e. not enough primary endpoint events), the key secondary endpoints will be evaluated and summarized using point estimates and associated 95% confidence intervals (without p-values).

The ordering of the secondary endpoints is as follows:

1) Composite endpoint of mortality and EQ5D index at Day 30 (QOL&M30)
2) Composite endpoint of mortality and EQ5D index at Day 90 (QOL&M90)
3) Primary endpoint at 45 days (CE45)

4) Primary endpoint at 90 days (CE90)
5) Venous events at 30 days (CEVTE30)
6) Arterial events at 30 days (CEATE30)

Using a fallback method the 0.05 type I error rate would be split as follows – 0.025, 0.005, 0.005, 0.005, 0.005, and 0.005. If QOL&M30 was statistically significant then QOL&M90 would be tested at 0.03 = 0.025 + 0.005. On the other hand, if QOL&M30 was NOT statistically significant then QOL&M90 would be tested at 0.005. The process would continue until all 6 secondary endpoints were tested. If the study does not accumulate enough CE30 events, it is expected that there would be limited information for secondary endpoints 3-6.
Statistical methods for testing the QOL&M30 and QOL&M90 endpoints will be based on a proportional odds model. The covariates in the model will include the participant's age (restricted cubic spline with 3 knots), sex, D-dimer (normal or abnormal), BMI (restricted cubic spline with 3 knots), antiplatelet usage (yes/no - at enrollment), WHO severity score (<five vs. ≥five), and the randomized treatment. The results of these models will be summarized using an odds ratio and associated 95% confidence interval.

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

Statistical methods for testing the secondary endpoints 3-6 listed above will follow the same procedures used for the primary endpoint described in Section 4.2 above. Except that for the CEVTE30 and CEATE30 events, an additional sensitivity analysis will be conducted by combining death from any causes to each one of the events separately.

4.4 SAFETY ANALYSES

The rates of safety outcomes listed in section 3.0.3 (e.g., ISTH major bleeding and the rate of ISTH CRNMB) during the 30-day treatment period and during the additional 60-day safety follow-up period between the two arms will be compared. The proportion of patients in each assigned treatment group who experience each safety event, the relative risk, and the absolute risk difference will be calculated from the observed data, and confidence intervals will be calculated. Analyses of the bleeding outcomes that occur during the full 90-day follow-up period (i.e., 30-day treatment period plus the 60-day safety follow-up) will also be conducted as part of the trial safety analyses. This analysis will be done for mITT population only (participants who had at least one dose of the drugs).

4.5 EXPLORATORY ENDPOINTS AND ANALYSES

Exploratory endpoints for this trial include the following.

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

For each of the above endpoints, the proportion achieving endpoints and the corresponding 95% confidence intervals will be presented by the treatment group using the Wald method and Clopper-Pearson exact intervals (Clopper and Pearson, 1934). Also, relative risk and the absolute risk differences with corresponding 95% confidence intervals will be estimated and presented.

Exploratory Analysis:
In order to get more insight into the treatment effect estimates, we will further analyze the data using Bayesian methods. More specifically, the likelihood of the observed data will be constructed assuming the random intercept log-binomial regression model described in Section 4.2. Conditional on the random effect for the site (γ), the unadjusted model can be written as

$$log(p) = \beta_0 + \beta_{treat} * Treat + \gamma,$$

where p is the probability of CE, $Treat$ is the treatment indicator (1 for treatment, and 0, for placebo), $\beta_0$is the logit of CE rate in the placebo group, β_{treat} is the log relative risk (RR) of the treatment compared to the placebo. The site random effect γwill be assumed to follow a normal distribution with mean zero and variance θ. For prior distributions, specifically of the effect of interest β_{treat}, we will follow the recommendations provided in Table 1 of the (Wijeysundera et al., 2009), where three types of priors were used: (i) flat uninformative - $\beta_{treat} \sim N(0, 100)$,(ii) Skeptical - $\beta_{treat} \sim N(0, \eta_1)$, where η_1 is such that the probability of achieving a benefit exceeding the assumed, that is, $\Pr(\beta_{treat} < \ln(0.65)) = 0.05$, and (iii) enthusiastic - $\beta_{treat} \sim N(\ln(0.65), \eta_2)$, where η_2 is such that the probability of no benefit $\Pr(\beta_{treat} > 0) = 0.05$. The prior distribution for the intercept β_0 is assumed non-informative with mean equal to the logit of the assumed placebo rate and standard deviation 10, and the variance component θ is assumed to follow a half-normal centered at 0 with standard deviation set to a 100 (Gelman, 2006). Prior distributions are assumed to be independent.

Marginal posterior distribution of the parameter β_{treat} is of interest. It will be calculated using the R package *brms (*Bürkner, 2017). Once the posterior distribution is computed, we will estimate two posterior quantities to help infer on the treatment effect: a) the probability of any benefit (OR<1, or equivalently, $\beta_{treat} < 0$), and b) the probability of exceeding the effects that were used for sample size calculation (RR<0.65 or equivalently, $\beta_{treat} < \ln(0.65)$).

4.6 SUB-GROUP ANALYSES

The primary analysis will be repeated within each of these subgroups. Interaction test-p-values will be obtained using log-binomial regression models. The pre-specified subgroups include:

- Antiplatelet usage (yes/no - at enrollment)
- WHO severity score (<five vs. ≥five)
- BMI (<30 vs. ≥30)
- D-dimer (normal or abnormal)
- ICU stay,
- Age (<40; 40-64; 65 and older),
- Sex, and
- Race/ethnicity.

4.7 REFERENCES

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4.8 APPENDICES

Appendix 1. ACTIV4C Roster of Statisticians

Team	Name	Email	Organization	Attends DSMB Meetings
Unblinded Statistical Team	Abdus S. Wahed	Wahed@pitt.edu	DCC	X
	James Troendle	james.troendle@nih.gov	NHLBI	X
	Lingyun Lyu	lil114@pitt.edu	DCC	
Blinded Statistical Team	Kevin Anstrom	kevin.anstrom@unc.edu	UNC	X
	Jungnam Joo	jungnam.joo@nih.gov	NHLBI	X
	Eric Leifer	leifere@nhlbi.nih.gov	NHLBI	X

Appendix 2. Abbreviated Monthly DSMB Tables on Safety and Efficacy Outcomes

A. PROTOCOL SUMMARY

B. CONSORT CHART

C. REPORTED SUSPECTED STUDY OUTCOMES

Table: Suspected Outcome Events among Randomized Subjects by Treatment

	All Randomized[1] (N=)		30 Days Follow Up[2] (N=)	
	ARM A (N=)	ARM B (N=)	ARM A (N=)	ARM B (N=)
Suspected Study Outcomes, n (%)				
Any Suspected Primary Outcome[3]				
Deep vein thrombosis of upper or lower extremities				
Pulmonary embolism				
Other venous thromboembolism				
Ischemic stroke				
Myocardial infarction				
Other arterial thromboembolism				
All-cause mortality				

[1]The number of all randomized participants.

[2]The number of 30 days follow up included participants who had 30 days of follow-up or withdrawn/dropped-out within 30 days.

[3]The primary study endpoint is defined as a composite endpoint of symptomatic deep vein thrombosis of upper or lower extremities, pulmonary embolism, other venous thromboembolism, ischemic stroke, myocardial infarction, other arterial thromboembolism, and all-cause mortality for up to 30 days after initiation of assigned treatment.

Figure: Kaplan-Meier Curves for the Time to Suspected Outcome Events

Note: The figure will include numbers at risk and number of events at designated timepoints, and will additionally include the KM estimates at days 30, 45, and 90 as inserts.

Table: Suspected Safety Outcome Events among Randomized Subjects by Treatment

	All Randomized (N=)		30 Days Follow Up (N=)	
	ARM A (N=)	**ARM B (N=)**	**ARM A (N=)**	**ARM B (N=)**
Bleeding, n (%)				

Figure: Kaplan-Meier Curves for the Time to Suspected Safety Outcome Events

D. ADJUDICATED STUDY OUTCOMES

Table: Adjudicated Outcome Events among Randomized Subjects by Treatment

	All Randomized[1] (N=)		30 Days Follow Up[2] (N=)	
	ARM A (N=)	ARM B (N=)	ARM A (N=)	ARM B (N=)
Study Outcomes, n (%)				
Any Primary Outcome[3]				
Deep vein thrombosis of upper or lower extremities				
Pulmonary embolism				
Other venous thromboembolism				
Ischemic stroke				
Myocardial infarction				
Other arterial thromboembolism				
All-cause mortality				

[1]The number of all randomized participants.

[2]The number of 30 days follow up included participants who had 30 days of follow-up or withdrawn/dropped-out within 30 days.

[3]The primary study endpoint is defined as a composite endpoint of symptomatic deep vein thrombosis of upper or lower extremities, pulmonary embolism, other venous thromboembolism, ischemic stroke, myocardial infarction, other arterial thromboembolism, and all-cause mortality for up to 30 days after initiation of assigned treatment.

Figure: Kaplan-Meier Curves for the Time to Adjudicated Outcome Events

Table: Adjudicated Safety Outcome Events among Randomized Subjects with 30-day Follow-Up by Treatment and adjudicated event data

	Arm A (N=XX)	**Arm B (N=XX)**
Major Bleeding, n (%)		
CRNMB, n (%)		
Minor bleeding, n (%)		

Figure: Kaplan-Meier Curves for the Time to Adjudicated Safety Outcome Events

Appendix 3. Detailed Tri-Monthly DSMB Tables on Safety and Efficacy Outcomes

In addition to the monthly abbreviated reports (Appendix 2), the following reports are made available to the DSMB every three months.

A. RECRUITMENT AND RETENTION STATUS

Figure: Site Activation by Month

Figure: Randomization by Month

Table: Numbers Consented and Randomized by Site

Sites and Networks	Consented	Randomized
Site 1		
Site 2		
..		

Table: Recruitment and Retention among Enrolling Sites

	Randomized	Discharged	Drug Start	Active	Limited Contact	Withdrawn	Day 30 Complete	Day 90 Complete
All Sites	N	N	n	N	N	N	N	n
Site 1	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Site 2	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
..	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**

Table: Visit Completion for Randomized Participants

	Randomized	Day 2	Day 10	Day 20	Day 30	Day 45	Day 90
Expected		**n**	**N**	**N**	**n**	**N**	**N**
Total	**N**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Site 1	N	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Site 2	N	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
..	N	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**

B. BASELINE CHARACTERISTICS

Table: Baseline characteristics of randomized participants

	Randomized	Arm A	Arm B
	N=	N=	N=
Stratification			
Antiplatelet Use (%)			
Hospitalization Severity (%)			
Severe			
Moderate			
Demographics			
Age (median (q1,q3))[1]			
Biological sex = Female (%)			
Race (%)			
White			
Asian			
Black or African American			
American Indian or Alaska Native			
Native Hawaiian or other Pacific Islander			
Aboriginal or First Nations			
Middle Eastern or North African			
More than one race			
Other race			
Unknown			
Ethnicity (%)			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown			
Medical History			
Cardiovascular			
Hypertension (%)			
Heart Failure			
Coronary Artery Disease (CAD)			
Peripheral Arterial Disease (PAD)			
Cerebrovascular Disease (stroke or TIA)			
Atrial fibrillation / flutter			
Deep Vein Thrombosis (DVT)			
Pulmonary Embolism (PE)			
Known thrombophilia			
Lower limb paralysis / paresis			
History of smoking and/or vaping			
None of the above			
Metabolic, Renal, or Digestive (%)			

Diabetes Type 1			
Diabetes Type 2			
Chronic Kidney Disease			
Liver Disease			
None of the above			
Respiratory (%)			
Asthma			
Chronic Obstructive Pulmonary Disease			
Interstitial Lung Disease			
Pulmonary Hypertension			
History of oxygen use prior to hospitalization			
None of the above			
Immunosuppressive Disease			
HIV/AIDS			
Metastatic Cancer			
Malignancy, receiving chemotherapy or immunotherapy			
History of cancer but not currently in treatment			
Leukemia			
Lymphoma			
Solid organ transplant			
Bone marrow transplant			
Autoimmune disease			
None of the above			
History of seizures			
History of alcoholism			
Current			
Former			
Never			
Unknown			
Baseline Medications			
Hydroxychloroquine / Chloroquine			
Colchicine			
Remdesivir			
IL6 Inhibitors			
Lopinavir / Ritonavir			
Interferon Beta-1a			
Convalescent Plasma			
Dexamethasone			
Azithromycin			
Other steroids (not Dexamethasone)			
Monoclonal Antibody			
Anticoagulants			
Anti-platelets			

IV argatroban continuous infusion			
IV argatroban continuous infusion			
IV bivalirudin continuous infusion			
IV unfractionated heparin infusion			
Unfractionated heparin subcutaneous			
Acenocoumarol			
Apixaban			
Dabigatran			
Dalteparin			
Edoxaban			
Enoxaparin			
Fluindione			
Fondaparinux			
Nadroparin			
Phenprocoumon			
Rivaroxaban			
Tinzaparin			
Warfarin			
Other anticoagulant			
Baseline Measures			
Contact Preference (%)			
Electronic Participant (ePPT)			
Telephone Participant (tPPT)			
Weight (kg) (median (q1,q3))			
BMI (median (q1,q3))			
Lab work (median (q1,q3))			
Albumin (g/dL)			
Alanine Transaminase (ALT) (U/L)			
Creatinine (mg/dL)			
D-Dimer (ug/L FEU)			
Hemoglobin (g/dL)			
Lactate Dehydrogenase (LDH) (U/L)			
Lymphocyte count (/mm^3)			
Neutrophil count (/mm^3)			
Platelets (10^3/uL)			
Sodium (mEq/L)			
Blood Urea Nitrogen (mg/dL)			
White Blood Cell (WBC) count (10^9/L)			
Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.7)			

q1=25th and q3=75th percentiles.

C. MEDICATION AND TREATMENT ADHERENCE

Table: Medication Adherence among Randomized Participants

	30 Days Follow Up[1] (N=)					
Missed Any Pills Since Last Follow Up	**n (%)**		**1~4 Pills**		**>4 Pills**	
	ARM A (N=)	**ARM B (N=)**	**ARM A (N=)**	**ARM B (N=)**	**ARM A (N=)**	**ARM B (N=)**
Follow Up at Day 10	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Follow Up at Day 20	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Follow Up at Day 30	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)

[1] The number of 30 days follow up include participants who had completed 30 days of follow-up or withdrawn/dropped-out within 30 days.

Table: Treatment Adherence among Randomized Participants

	30 Days Follow Up[1] (N=)	
	Arm A (N=)	**Arm B (N=)**
Treatment Ever Interrupted, N (%)		
Number of Interrupted Days	n (%)	
..		
..		
..		
Treatment Stopped Permanently, N (%)		
Reasons	n (%)	
…		

[1] The number of 30 days follow up include participants who had completed 30 days of follow-up or withdrawn/dropped-out within 30 days.

D. SERIOUS ADVERSE EVENTS LISTINGS:

All serious adverse events (SAEs) that occurred between the previous DSMB and current DSMB data freeze dates are listed by treatment arms. Following information is provided for each SAE.

PATID:
Case x of x
Event Onset Date:
Expected/Relatedness: Unexpected and Unrelated to Study Medication
Randomization Date:
Study Medication Day:
Reported Event:
Recovery Status:
Narrative:

E. PROTOCOL DEVIATIONS

All protocol deviations are listed in this section.