Comparison of **H**eparin **A**ssay **M**onitoring **P**rotocols (CHAMP)
Statistical Analysis Plan

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Introduction

Unfractionated heparin (UFH) is the most widely used intravenous (IV) anticoagulant for the treatment and prevention of thromboembolic disease. Indications for use of UFH include venous thromboembolism, acute coronary syndrome, and acute ischemic stroke. UFH is used to prevent thrombosis in the setting of arrhythmias, extracorporeal membrane oxygenation (ECMO), cardiopulmonary bypass (CPB), and endovascular procedures. The unpredictable pharmacokinetics of UFH and interpatient variability result in a narrow therapeutic index restricting its use to the hospital setting with close monitoring and adjustments (1).

Two validated assays exist and are in use at the Vanderbilt University Medical Center (VUMC) adult hospital for the monitoring of UFH: (1) the activated partial thromboplastin time (aPTT), and (2) the chromogenic anti-factor Xa assay (anti-Xa). At VUMC, the aPTT protocol is managed by nursing, while the anti-Xa protocol is managed by clinical pharmacy. Both are clinically acceptable methods for titration and adjustment of UFH.

It is hypothesized that using the anti-Xa protocol to monitor heparin will lead to a shorter time to reach therapeutic anticoagulation range, but to the best of our knowledge, aPTT and anti-Xa UFH monitoring protocols have not been compared in a prospective, randomized clinical trial. This document describes the statistical analysis plan (SAP) for a pragmatic, randomized clinical trial comparing the effectiveness of the two UFH monitoring protocols for systemic anticoagulation in hospitalized adult patients. This SAP has been prepared prior to locking the final dataset.

Study Population

Adults aged 18 years and older who are admitted as observation or inpatients at Vanderbilt University adult hospital for whom IV UFH on the standard aPTT protocol is ordered are considered potentially eligible for the trial. Patients who meet inclusion and exclusion criteria below will be enrolled and randomized to one of two study arms: aPTT guided arm or anti-Xa guided arm.

Inclusion:

- Patients age 18 years and older who are admitted as observation or inpatients for whom IV UFH (monitored via the aPTT nurse-managed protocol) is ordered
- Baseline aPTT value is ≥0 and ≤ 36.0 seconds
- Baseline heparin level anti-Xa assay value is ≥0 and ≤0.3 IU/mL

Exclusion:

- Indication for anticoagulation is ECMO or cerebrovascular ischemic event
- Provider determines patient is not appropriate for the study

Patients who are excluded from the study will remain ineligible for the duration of that encounter. A subset of patients may be readmitted and receive UFH during the study period. In these instances, since the outcomes are collected only during the index hospitalization, if the patient meets inclusion criteria and does not meet exclusion criteria, the patient will be randomized again, and the readmission will be considered a new instance/encounter. Patients whose heparin is discontinued and re-initiated within the same encounter will not be re-randomized.

Interventions

aPTT guided arm: Patients in the aPTT guided arm will be monitored using the nurse managed aPTT guided protocol (stratified by low dose and high dose protocols).

Anti-Xa guided arm: Patients in the anti-Xa guided arm will be monitored using the pharmacy managed anti-Xa protocol (stratified by low dose and high dose protocols).

Study Endpoints

Observation Period

The major endpoints including the primary and secondary endpoints will be measured during the same observation period defined as the time from initiation of the heparin infusion through the first time when the heparin protocol is discontinued. When this observation period is different for some endpoints (e.g., the safety endpoints), a specific timeframe of the observation period is specified under each endpoint as appropriate.

Primary Endpoint

The primary endpoint is time to first reach therapeutic (anticoagulation) range by coagulation assay from the time of intravenous heparin initiation. By definition, every patient begins out of therapeutic range. As heparin takes effect very quickly, it can be presumed that patients found to be in therapeutic range became so shortly after their heparin was administered or adjusted. Patients found to be in therapeutic range at the first lab measurement will be considered to reach therapeutic range 10 minutes after the heparin infusion initiation. Patients found to be in therapeutic range at subsequent measurements will be considered in range 10 minutes after the last heparin infusion rate adjustment.

Secondary Effectiveness Endpoints

1. Percent of laboratory measurements (aPTT or anti-Xa) within the therapeutic range, as defined by protocol
2. The total number of coagulation laboratory measurements for overall in-hospital coagulation time
3. The total number of heparin rate changes for overall in-hospital coagulation time

Secondary Safety Endpoints

The incidence of following outcomes:

1. New thrombotic events on anticoagulation or within 24 hours of anticoagulation cessation (Yes/No)
2. Any clinically relevant bleeding adverse events (Yes/No), defined as:
    a. Fatal bleeding, or
    b. Overt bleeding events causing a decline in hemoglobin >2 g/dL over a 24-hour period, or
    c. Bleeding leading to transfusion of two or more units of whole blood or red blood cells, within 48 hours of anticoagulation cessation, or
    d. Intracranial bleeding events
3. Any new thrombotic events on anticoagulation or any clinically relevant bleeding adverse events as defined above (Yes/No)

Exploratory Endpoints

1. Time on heparin drip protocol out of therapeutic range for overall in-hospital coagulation time. As with the primary outcome, all patients will begin out of therapeutic range starting at the time of heparin infusion initiation. Patients will be considered out of therapeutic range until a lab result shows they are within range, and vice versa. Patients whose first lab measurement is within therapeutic range will be considered in range starting 10 minutes after heparin infusion initiation. Patients who were previously out of range and become in range following an infusion rate adjustment will be considered in range beginning 10 minutes after the most recent rate change. Patients with a lab measurement out of therapeutic range after previously being in range will be considered out of range from the time the lab specimen was taken.
2. Reaching therapeutic range by first measurement, second measurement, and within 24 hours after initiation. Each of these is a binary outcome (Yes/No), assessed cumulatively.
3. UFH dosing (units/kg/hr and units/hr) at time of reaching therapeutic range, for patients who reach therapeutic range.
4. Protocol compliance (Yes/No). Protocol compliance definitions are provided in **Appendix A**.
5. Adjusted scale of anticoagulation time measurements: The following measures will be evaluated using an adjusted scale for anti-Xa and aPTT values, designed to align their ranges for comparability. On this scale, a value of zero (the midpoint of the therapeutic range) represents the optimal clinical status, with deviations in either direction indicating worsening conditions. Details of the adjusted scale are provided in **Appendix B**.
    a. Root mean squared difference from zero on the adjusted scale
    b. Mean absolute difference from zero on the adjusted scale

Fidelity Endpoints

1. Overall heparin protocol compliance during the first week on heparin drip protocol. The metrics for intervention fidelity are readily available as laboratory measurements in the electronic health record (EHR) and are tracked by the anticoagulation oversight committee through a Quality Safety and Risk Prevention (QSRP) dashboard. These metrics include protocol compliance to bolus order, aPTT or anti-Xa level drawn within time window, rate change, repeat aPTT or anti-Xa level, and stop or held infusion. Overall protocol compliance will be defined as meeting all compliance criteria during this time period. Protocol compliance definitions are provided in **Appendix A**.
2. Crossover between protocols will be captured.

Design Considerations

Study Design

This study is designed as a pragmatic, single center, randomized controlled trial comparing the effectiveness of the aPTT and anti-Xa protocols for optimal monitoring of IV UFH for systemic anticoagulation in hospitalized adult patients.

Randomization

Eligible patients will be randomized in a 1:1 ratio to the aPTT guided arm or the anti-Xa guided arm. Randomization will occur once at the encounter level. The study arm assignments will be

performed by computerized randomization using EPIC functionality. As patient characteristics can necessitate either a high or low dose heparin protocol, patients will be stratified by high and low dose in order to reflect typical ratios of high and low dose heparin protocols in clinical practice, and the randomization to study arms will be performed within each stratum.

Clinical Trial Design and Operating Characteristics

We developed a Bayesian sequential clinical trial design to compare two coagulation assay methods (i.e., the aPTT guided arm and the anti-Xa guided arm) through simulation studies using preliminary data collected during the six months preceding study initiation. The maximum sample size is set at 700 over a 24-month study period, based on the estimated enrollment rate of approximately 30 eligible patients per month.

One interim analysis will be conducted in a blinded manner within the Bayesian framework after 500 patients have been enrolled, with the final analysis planned at the full sample size of 700 patients enrolled. At the interim analysis, an efficacy stopping rule will allow early termination if there is sufficient evidence favoring one arm over the other, while a separate non-binding futility rule will allow early termination if the trial shows little promise of success (see *Interim Analysis* section for details).

Figure 1 presents the operating characteristics of the design: the red line denotes the type I error rate, and the other curves represent power to detect superiority of one arm over the other across a range of true hazard ratios (HRs).

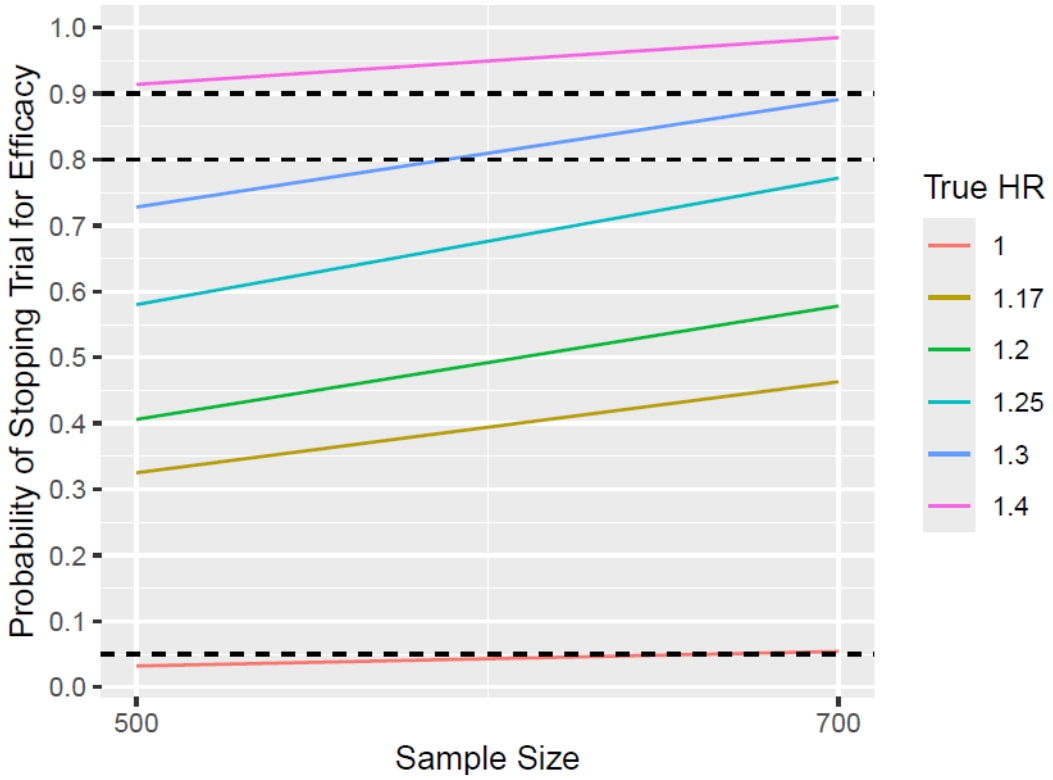

Figure 1. Operating Characteristics of Bayesian Sequential Clinical Trial Design.

Statistical Approach

General Approach
The interim and main analyses for the primary endpoint will be conducted using a Bayesian approach, while all other analyses will be performed within a frequentist framework. We do not expect the proportion of patients who are readmitted and randomized again to be large, and thus any impact on statistical inference should be minimal. However, if this proportion is higher than anticipated (e.g., exceeds 10%), we will account for the resulting repeated measurements using a longitudinal analysis method as a sensitivity analysis.

Analysis Set
The Full Analysis (FA) Set will include all randomized participants who are eligible and did not meet exclusion criteria specified in the study protocol. All statistical analyses will be performed using the FA Set with the study arms as originally assigned, even if participants randomized to anti-Xa guided arm never initiate anti-Xa protocol (i.e., these participants remain on the aPTT protocol) or if the participants in the aPTT protocol get switched to anti-Xa monitoring for clinical purposes.

Interim Analysis
We will conduct one interim analysis in a blinded manner after 500 patients have been enrolled and their primary endpoint data have been completely collected. At this interim, a Bayesian survival analysis for the primary endpoint will be performed. A skeptical prior will be placed on log HR, the parameter of interest for comparing the two arms, specified as a normal distribution with mean 0 and standard deviation 0.35. This prior reflects the belief that extreme effects are unlikely, corresponding to a 5% probability that HR > 2 or HR < 0.5. We will also calculate the posterior predictive probability of success at the final analysis given the interim data, where success is determined if the predictive probability that HR < 1 exceeds 0.975 or the predictive probability that HR > 1 exceeds 0.975 at the planned maximum sample size. At the interim analysis, two rules will be applied:

1. **Efficacy stopping rule (binding)**: The trial will be stopped early for superiority of one arm over the other if the posterior probability that HR > 1 exceeds 0.975 or the posterior probability that HR < 1 exceeds 0.975.
2. **Futility decision rule (non-binding)**: A decision to enroll the remaining patients up to the sample size of 700 will be guided by the posterior predictive probability of success. If this probability is less than 0.20 at the planned maximum sample size, the trial will be considered futile. Because this rule is non-binding, the final decision at the interim will take into account the totality of evidence.

If the trial is not stopped at the interim, enrollment will continue until the maximum sample size of 700 patients is reached.

Descriptive Analysis
Categorical variables will be described using frequencies and proportions, and continuous variables will be described using means and standard deviations, as well as medians and interquartile ranges (IQR). Missingness will be reported for each variable. Graphical summaries may be used to describe the data graphically. No statistical comparisons between the study arms

will be performed for the descriptive analysis.

Baseline demographic and clinical data: To characterize the study sample, baseline demographic and clinical data will be described overall and by the study arm. At a minimum, the following variables will be described at time of enrollment:

- Age (years)
- Sex at birth (male, female, unknown)
- Patient-reported race (White, African American, Asian/Pacific Islander, Multiple, Native American, Other, Unknown)
- Patient-reported ethnicity (Hispanic, Non-Hispanic, Unknown)
- BMI (kg/m^2)
- Baseline Sequential Organ Failure Assessment (SOFA) score (value closest to time of randomization)
- Elixhauser comorbidity score (value closest to time of randomization)
- Liver disease (Yes/No)
- Baseline hemoglobin (Hgb [gm/dL]) (value closest to time of randomization)
- Baseline platelet count (value closest to time of randomization)
- Heparin target dose ordered at baseline (e.g., high dose or low dose)

Secondary safety endpoints, the exploratory endpoints, and fidelity endpoints: The descriptive analysis will be performed by the study arm as well as low vs. high dose heparin protocol.

Main Analysis
Primary endpoint: A survival analysis using a Bayesian approach will be conducted to assess whether the time to reach the therapeutic anticoagulation range differs between the aPTT guided and anti-Xa guided arms. The analysis will adjust for the following covariates: age, sex, race, ethnicity, BMI, baseline SOFA score, Elixhauser comorbidity score, duration of heparin protocol (≥24 hours vs. <24 hours), and baseline heparin target dose (high vs. low). A skeptical prior (as defined in the Interim Analysis section) will be placed on the parameter for treatment arm assignment, while weakly informative priors will be used for all other parameters. Results will be summarized using posterior means and 95% credible intervals (CIs). In addition, Kaplan-Meier curves will be presented to visualize differences in the primary endpoint between the two arms.

Secondary effectiveness endpoints: Analyses of the secondary effectiveness endpoints will be conducted using generalized linear models with appropriate link functions, within a frequentist framework, adjusting for the same covariates listed above. For analyses of the number of coagulation laboratory measurements and the number of heparin rate changes, overall in-hospital anticoagulation time will be included as an offset term to account for differences in duration of observation.

Handling Intercurrent Events
The death rate is expected to be very low. If death occurs, it will be handled using *while on treatment strategy*.

Handling Missing Data

We do not anticipate missing data for the primary or secondary endpoints. For missing covariates, if the proportion of missing values for a given covariate is less than 5%, single imputation will be applied. If more than 5% of values are missing, missing covariates will be addressed using a Bayesian approach or multiple imputation will be employed.

Differential Treatment Effects
To assess whether the effect of two coagulation assay methods on outcomes is modified by patient characteristics, interaction terms between study arm assignment and each of the following variables will be included in the models for the primary and secondary outcomes:

- Baseline heparin target dose (low- versus high-dose)
- Duration of heparin protocol (≥24 hours versus <24 hours)
- Baseline SOFA score

For SOFA score, a sensitivity analysis will be conducted to evaluate potential nonlinearity. Unless there is evidence for nonlinearity, the model will assume a linear interaction between study arm assignment and SOFA score.

Subgroup Analysis
Subgroup analyses of the primary and secondary effectiveness endpoints will be conducted for patients on low- versus high-dose heparin protocols, as well as for patients with protocol duration ≥24 hours versus <24 hours, if sufficient evidence supports differential treatment effects in these groups.

Appendix A

Heparin Protocol Compliance Definitions

Rate Change Window (Hours):
Hour difference between rate change time in MAR and heparin lab (aPTT or anti-Xa) result time. This is only showing the rate change occurred within 4 hours of heparin lab result time.

Rate Change By (units/kg/hr):
Difference between the rate for "Rate Change" and "Rate/Dose Change" MAR action and the rate before specimen was taken.

Rate Change Compliance:
Y (Yes) if rate change amount follows protocol and rate change window is within 2 hours of heparin lab result time.
NA (Not Applicable) if rate doesn't need change per protocol or order was discontinued within 4 hours of heparin lab result time.

Stop Infusion Compliance:
Y (Yes) if infusion is stopped within 2 hours of heparin lab result time.

Repeat Heparin Lab:
Y (Yes) if there is a subsequent repeat heparin lab per protocol based on heparin lab value.
NA (Not Applicable) if order was discontinued within 8 hours of heparin lab Result Time.

Heparin Lab Window (Hours):
Hour difference between heparin lab Specimen Taken Time and Initial Infusion Time (if first heparin lab), Rate Change Time (when present) or the previous Specimen Taken Time (if no rate change).

Heparin Lab Within Time Window:
Y (Yes) if heparin lab specimen Taken Time is within 4-8 hours after Initial Infusion Time (if first heparin lab), Rate Change Time (when present) or the previous Specimen Taken Time (if no rate change).
NA (Not Applicable) if patient went to OR.

Exception:

1. For heparin lab with the criteria below, after 2 consecutive therapeutic heparin labs, check heparin lab window for 4-36 hours.
    - aPTT low dose protocol: aPTT between 60 and 80
    - aPTT high dose protocol: aPTT between 60 and 110
    - anti-Xa low dose protocol: anti-Xa between 0.3 and 0.7
    - anti-Xa high dose protocol: anti-Xa between 0.3 and 0.5
2. For aPTT with the criteria below, check aPTT window for 5-9 hours (to count for the 1 hour stop time).
    - aPTT low dose protocol: aPTT >between 111 and 199
    - aPTT high dose protocol: aPTT between 151 and 199

3. For heparin lab with the criteria below, check heparin lab window for 0-3 hours.
    - aPTT low dose protocol: aPTT > 199 (check aPTT window for 0-3 hours until <110.5)
    - aPTT high dose protocol: aPTT > 199
    - anti-Xa low dose protocol: anti-Xa > 1.0
    - anti-Xa high dose protocol: anti-Xa > 1.0

<u>Bolus Order Compliance:</u>
Y (Yes) if Bolus was administered within 2 hours of heparin lab Result Time or order was discontinued within 4 hours of heparin lab Result Time.

Appendix B

Adjusted Scale of Anticoagulation Time Measurements

The clinical order guideline defines assay ranges differently for anti-Xa levels (0.2–1.0) and aPTT values (40–200), making them not directly comparable. To align these measures approximately (see **Figures A1** and **A2**), anti-Xa values were rescaled by multiplying the raw values by 200. Next, the final scale was centered by subtracting the midpoint of each therapeutic range: 85 and 70 for aPTT (high- and low-dose, respectively), and 100 (=0.5×200) and 80 (=0.4×200) for anti-Xa (high- and low-dose, respectively). As shown in **Figure A3 (A)**, a value of zero represents the center of the therapeutic range (i.e., the optimal clinical status), with deviations in either direction indicating worsening conditions. In addition, ordinal scores based on the clinical algorithm can be derived, as illustrated in **Figure A3 (B)**.

Higher Dose (DVT/PE, valve)

- Initial bolus: 80 units/kg (MAX: 10,000 units)
- Initial infusion: 18 units/kg/hr (MAX: 2000 units/hr)
- PTT goal range: 60-110 seconds
- Enter order and obtain STAT PTT 6 hours after initiation of infusion.

PTT value	Protocol Instructions
Less than 40	• Increase infusion by 4 units/kg/hr from previous rate • Order bolus of 80 units/kg • Repeat STAT PTT 6 hours after rate change
40-59	• Increase infusion by 2 units/kg/hr from previous rate • Order bolus of 40 units/kg • Repeat STAT PTT 6 hours after rate change
60-110	• Infusion unchanged from previous rate • Repeat STAT PTT in 6 hours • After 2 consecutive therapeutic PTTs, obtain PTT q24h
111-150	• Decrease infusion by 2 units/kg/hr from previous rate • Repeat STAT PTT 6 hours after rate change
151-199	• **Stop infusion for 1 hour** • Decrease infusion by 2 units/kg/hr from previous rate • Repeat STAT PTT 6 hours after rate change
Greater than 199 ***Alert Provider***	• Step 1: **Stop infusion** and notify provider, even if contamination suspected. • Step 2: Repeat STAT PTT q2h from previous draw time until <111 ○ **If contamination suspected, repeat STAT PTT without waiting 2 hours** • Step 3: Once PTT < 111, **decrease infusion by 4 units/kg/hour from previous rate documented on MAR** • Step 4: Repeat STAT PTT 6 hours after rate change •

High-Dose Heparin Algorithm—With Bolus (DVT, PE, Valve)

- Initial bolus: 80 units/kg (MAX: 10,000 units)
- Initial rate: 18 units/kg/hour (MAX: 2000 units/hour)
- Anti-Xa goal: 0.3 to 0.7 IU/mL
- Enter order for STAT UFH level 6 hours after initiation of infusion.

UFH level	Titration Recommendation
≤0.2	Increase rate by 4 units/kg/hour from previous rate. Bolus 50 units/kg. Repeat STAT UFH level 6 hours after dose change.
0.21—0.29	Increase rate by 2 units/kg/hour from previous rate. Bolus 40 units/kg. Repeat STAT UFH level 6 hours after dose change.
0.3—0.7	Continue same rate and recheck STAT UFH level in 6 hours. When two consecutive UFH levels return within the therapeutic range, recheck UFH levels every 24 hours.
0.71—1.0	Decrease rate by 2 units/kg/hour from previous rate. Repeat STAT UFH level 6 hours after dose change.
>1.0 ***Notify Provider***	**Step 1: Stop infusion and repeat STAT UFH level every 2h from previous draw time until <1.0 IU/mL.** • **If contamination suspected, repeat STAT UFH level without waiting 2 hours** Step 2: After UFH level < 1.0, decrease rate by 4 units/kg/hour less than previous rate. Step 3: Repeat STAT UFH level 6 hours after rate change

Figure A1. High Dose Heparin Order Guideline. Assay names in the figure reflect their clinical labels in the VUMC EHR. PTT denotes aPTT and UFH denotes anti-Xa.

Lower dose (ACS, Atrial fibrillation)

- Initial bolus: 60 units/kg (MAX: 4,000 units)
- Initial infusion: 12 units/kg/hr (MAX: 1000 units/hr)
- PTT goal range: 60-80 seconds
- Enter order and obtain STAT PTT 6 hours after initiation of infusion.

PTT value	Protocol Instructions
Less than 40	• Increase infusion by 4 units/kg/hr • Order bolus of 60 units/kg • Repeat STAT PTT 6 hours after rate change
40-59	• Increase infusion by 2 units/kg/hr • Order bolus of 30 units/kg • Repeat STAT PTT 6 hours after rate change
60-80	• Infusion unchanged • Repeat STAT PTT in 6 hours • After 2 consecutive therapeutic PTTs, obtain PTT q24h
81-110	• Decrease infusion by 2 units/kg/hr • Repeat STAT PTT 6 hours after rate change
111-199	• **Stop infusion for 1 hour** • Decrease infusion by 3 units/kg/hr • Repeat STAT PTT 6 hours after rate change
Greater than 199 ***Alert Provider***	• **Stop infusion and repeat STAT PTT q2h from previous draw time until <111** • After PTT < 111, decrease infusion by 4 units/kg/hour less than previous rate. • Repeat STAT PTT 6 hours after rate change • If contaminated sample suspected, repeat STAT PTT • If contamination is ruled out, notify provider immediately of high PTT level.

Low-dose Heparin Algorithm – With Bolus (ACS, AF)

- Initial bolus: 60 units/kg (Max: 4000 units)
- Initial rate: 12 units/kg/hour (MAX: 1000 units/hour)
- Anti-Xa goal: 0.3 to 0.5 IU/mL
- Enter order for STAT UFH level 6 hours after initiation of infusion.

UFH level	Titration Recommendation
≤0.2	Increase rate by 4 units/kg/hour from previous rate. Bolus 40 units/kg. Repeat STAT UFH level 6 hours after dose change.
0.21—0.29	Increase rate by 2 units/kg/hour from previous rate. Bolus 30 units/kg. Repeat STAT UFH level 6 hours after dose change.
0.3—0.5	Continue same rate and repeat STAT UFH level in 6 hours. When two consecutive UFH levels return within the therapeutic range, recheck UFH levels every 24 hours.
0.51—0.7	Decrease rate by 2 units/kg/hour from previous rate. Repeat STAT UFH level 6 hours after dose change.
0.71 —1.0	**Stop infusion for 1 hour.** Decrease rate by 3 units/kg/hour from previous rate. Repeat STAT UFH level 6 hours after dose change.
>1.0 ***Notify Provider***	**Step 1: Stop infusion and repeat STAT UFH level every 2h from previous draw time until <1.0 IU/mL.** • **If contamination suspected, repeat STAT UFH level without waiting 2 hours** Step 2: After UFH level < 1.0, decrease rate by 4 units/kg/hour less than previous rate. Step 3: Repeat STAT UFH level 6 hours after rate change

Figure A2. Low Dose Heparin Order Guideline. Assay names in the figure reflect their clinical labels in the VUMC EHR. PTT denotes aPTT and UFH denotes anti-Xa.

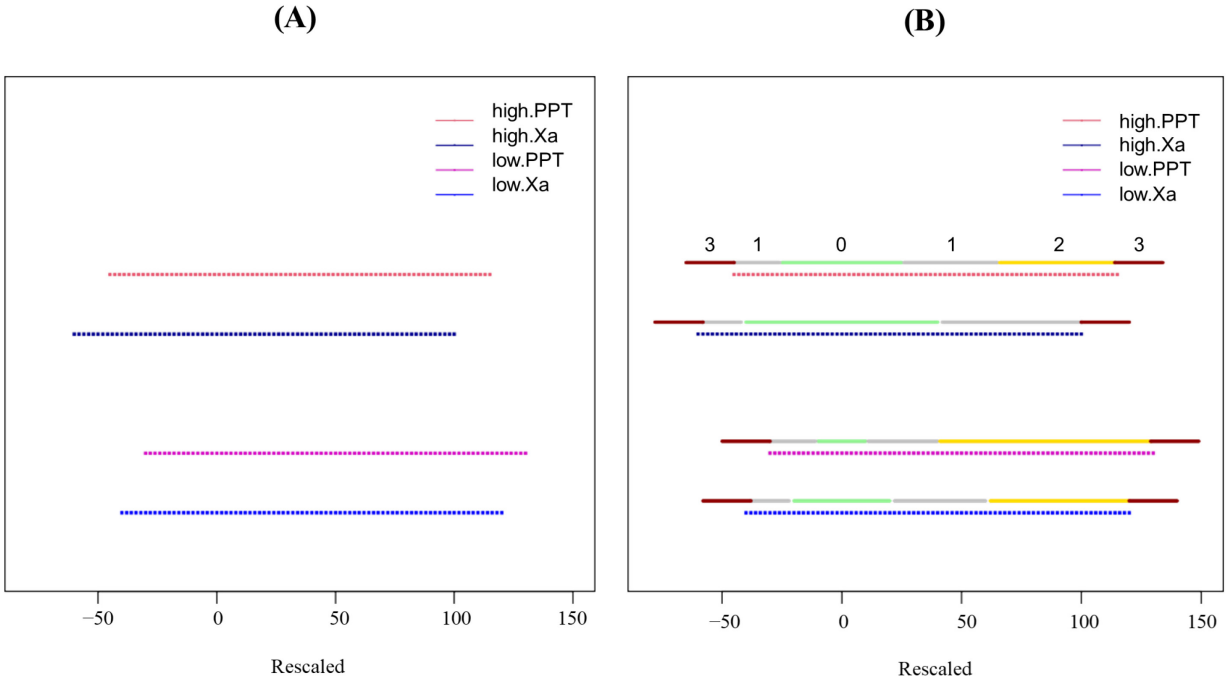

Figure A3. Adjusted Scale of Anticoagulation Time Measurements. (A) The adjusted scale showing centered aPTT values and rescaled, centered anti-Xa values. **(B)** Ordinal scores (color-coded categories ranging from 0 to 3) based on the clinical algorithm (see Figures A1 and A2), overlaid on the adjusted scale. A value of zero (the center point of the therapeutic range) represents the optimal clinical status, with deviations in either direction indicating worsening conditions; a score of 3 indicates the most severe status. PTT denotes aPTT and Xa denotes anti-Xa.

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