Supplementary Online Content

Study Protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

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PROTOCOL TITLE

Evaluation of Venous Thromboembolism Prevention in High-Risk Trauma Patients: A Prospective, Randomized Trial of Standard Enoxaparin Versus Two Anti-Xa Adjusted Dosing Strategies

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INTRODUCTION

Abstract/Brief Overview

Venous thromboembolism (VTE) is a common, potentially life-threatening complication in high-risk trauma patients. With emerging evidence demonstrating around 50% of trough serum anti-factor Xa (anti-Xa) concentrations are subtherapeutic and associated with increased VTE risk, the purpose of this pilot study is to evaluate the safety and efficacy of a novel enoxaparin dosing strategy based on anti-Xa values. High-risk patients (e.g., risk assessment profile score ≥ 5) initiated on enoxaparin 30 mg q12h per current trauma team standard of care. Patients will be excluded for renal dysfunction (Cockcroft-Gault calculated creatinine clearance < 30 mL/min or patients on continuous renal replacement therapy), weight < 50 kg or > 150 kg, nephrotic syndrome, platelet count < 50 x 10^3, allergy to heparin, patients on or requiring therapeutic anticoagulation at or within 24 hours of admission, isolated intracranial hemorrhage, known hyperbilirubinemia, pregnancy, or incarceration. Primary outcome is the comparison of antithrombin-III (AT-III), proportion of anti-Xa goal achievement at first, second, and all assessments, and time to goal anti-Xa. Patient outcomes include VTE events, bleeding outcomes, patients with bioaccumulation, and risk factors for low anti-Xa.

Purpose of Study

The purpose of this pilot study is to compare two enoxaparin dosing strategies: BID dosing and a dosing strategy based on anti-Xa values in high-risk trauma patients. Specific aims include: 1) to compare the extent of reduced AT-III activity between patients with anti-Xa ≥ 0.1 IU/mL and < 0.1 IU/mL upon initial assay and determine the proportion of patients who reach goal anti-Xa and time to goal anti-Xa between two dosing strategies: enoxaparin 40 mg every 12 hours (with consideration to increase to 50 mg every 12 hours if recheck anti-Xa is not at goal; see section 6) and enoxaparin 30 mg every eight hours; 2) to compare anti-Xa adjusted enoxaparin-dosing strategies based on VTE, bleeding rates, transfusion requirements, drug discontinuation rate and bioaccumulation, and 3) to determine patient-specific factors that correlate to subtherapeutic anti-Xa such as serial AT-III activity, weight, body mass index, age, cumulative fluid administration and thromboelastography (TEG).

Background

Background and Significance

Venous thromboembolism (VTE) is a common and potentially life-threatening complication in hospitalized patients. VTE risk is highest in the subset of critically injured patients, with the estimated incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) without prophylaxis ranging from 40-80% and 4-10%, respectively.[1] Low molecular weight heparin (LMWH) agents are the agent of choice for VTE prevention in high-risk trauma patients (i.e., multiple orthopedic trauma; injury severity score [ISS] > 9).[2-9]

Enoxaparin is a LMWH that is FDA-approved for the treatment and prevention of VTE. Enoxaparin binds to and potentiates the action of anti-thrombin III (AT-III). AT-III is an endogenous anticoagulant that inhibits factors Xa and IIa (e.g., thrombin) to prevent clot formation. Conflicting evidence exists for the optimal enoxaparin dose in critically injured patients. Trough serum anti-factor Xa (anti-Xa) concentrations between 0.1 – 0.2 IU/mL have been utilized as a surrogate marker for LMWH prevention efficacy.[10] A single-center, prospective, observational study of high-risk (ISS > 10) edematous (n = 10) and non-edematous (n = 11) trauma patients receiving enoxaparin 30 mg every 12 hours demonstrated proportion of anti-Xa < 0.1 IU/mL at 4, 8, and 12 hours were 60%, 90%, and 100%, respectively, in edematous patients. Even 64% and 81% of non-edematous patients were undetectable at 8 and 12 hours.[11] Calculated mean enoxaparin half-lives for edematous and non-edematous patients were 0.83 ± 0.51 hours and 1.85 ± 0.93 hours, respectively (p = 0.014), which suggests rapid elimination of enoxaparin. Rutherford[12] similarly evaluated anti-Xa values in seventeen critically ill surgery and trauma patients receiving enoxaparin 40 mg every 24 hours. Mean steady state four-hour peak anti-Xa was 0.19 ± 0.09 IU/mL while the mean trough was 0.04 ± 0.04 IU/mL. Fifteen (88%) patients had a trough anti-Xa ≥ 0.1 IU/mL with five (29%) patients having a trough anti-Xa of zero. If anti-Xa provides a marker for efficacy, the above results suggest enoxaparin 30 mg every 12 hours and 40 mg every 24 hours will not provide adequate VTE prophylaxis. Only one retrospective review has evaluated VTE events between enoxaparin 30 mg every 12 hours and 40 mg every 24 hours, which was not statistically significant (1.1% vs. 2.9%, p = 0.118).[13]

Robinson[14] performed a prospective, randomized trial following serial anti-Xa levels at baseline, 4, 12, 16, and 24 hours for three days in medical/surgical ICU patients receiving enoxaparin 40 mg once daily versus 30 mg twice daily, 40 mg twice daily, or 1 mg/kg once daily. Majority of patients (88%) were admitted for medical, not surgical, diagnoses. An anti-Xa between 0.1 – 0.4 IU/mL was maintained for 33.3% in 40 mg daily group, 41.7% in 30 mg twice-daily group, 83% in 1 mg/kg daily group, and 91.7% in 40 mg twice-daily group of the study period. Mean steady-state peak anti-Xa levels were 0.13 IU/mL for 40 mg daily, 0.15 IU/mL for 30 mg twice daily, 0.33 IU/mL for 40 mg twice daily, and 0.40 IU/mL for 1 mg/kg daily. The authors concluded that enoxaparin 40 mg daily and 30 mg twice daily may provide insufficient VTE prophylaxis, but the ideal dose is still unknown.

Increased VTE rates have been seen in patients with subtherapeutic anti-Xa values. Malinoski[15] found that of 54 patients on enoxaparin 30 mg every 12 hours, 27 (50%) had subtherapeutic anti-Xa troughs and a statistically significant higher DVT rate than those with appropriate levels (37% vs. 11%, p = 0.026). Mean peak anti-Xa values were also lower in the subtherapeutic group (0.17 ± 0.1 IU/mL vs. 0.27 ± 0.1 IU/mL, p < 0.001); however, peak anti-Xa values were not different in those with and without DVT (0.23 ± 0.12 IU/mL vs. 0.23 ± 0.1 IU/mL, p = NS). A subsequent enoxaparin anti-Xa dose-adjusted protocol targeting peak anti-Xa levels between 0.2 – 0.4 IU/mL showed 18 (29.5%) of 61 patients on 30 mg twice-daily enoxaparin were at goal anti-Xa after the third dose.[16]Only 5 (8.2%) patients, all in the therapeutic peak anti-Xa group, had a trough anti-Xa > 0.1 IU/mL. VTE events occurred in three patients in the entire study cohort (4.9%). Of the 27 patients with dosage adjustments, 22 (81.5%) patients received enoxaparin 40 mg twice daily, four patients received 50 mg twice daily (14.8%), and 1 patient received 60 mg twice daily (3.7%). Of note, there were no major bleeding events, which is not surprising given the anti-Xa peak goal is much lower when compared to standard therapeutic dosing goals (e.g., 0.5 – 1.1 IU/mL). Finally, a before-and-after study evaluated an anti-Xa adjusted dalteparin dosing strategy in high-risk (risk assessment profile [RAP] ≥ 5) trauma patients.[17] High-risk patients were initiated on dalteparin 5000 units daily with a 12-hour anti-Xa value drawn after the first dose in the post-protocol group. If the 12 hour anti-Xa was < 0.1 IU/mL, the dose was increased to 5000 units twice-daily. Low trough anti-Xa was seen in 51% of post-group patients. VTE was lower in the post-protocol group (7.0% vs. 12.8%, p = 0.009) and higher in the subgroup of patients with a subtherapeutic trough anti-Xa (14.4% vs. 5.4%, p = 0.05). Therefore, anti-Xa adjustment of LMWH may result in fewer VTE events. No difference in blood transfusion after the first 48 hours was noted, suggesting appropriate safety with an anti-Xa driven dosing protocol for dalteparin.

Previous studies have tried to identify predictors for low anti-Xa concentrations. Young age, high body weight, edema, and low peak anti-Xa concentration have been associated with low trough anti-Xa.[11, 15, 17] AT-III concentrations have not been collected or evaluated in many previous studies. Low AT-III concentrations have not been evaluated as a risk factor for low anti-Xa. Theoretically, low serum AT-III may represent a reduction in substrate to which LMWH can bind and exert anticoagulant effects. Hence, LMWH effectiveness and anti-Xa may be reduced.

Pharmacokinetic / Safety Information

Previous pharmacokinetic studies evaluating enoxaparin prophylaxis and anti-Xa levels suggest high inter-patient variability, especially in critically ill patients (table 1).[11-12,14] However, the mean maximum serum concentration (Cmax) did not reach the lower threshold for therapeutic dosing. Therapeutic enoxaparin anti-Xa concentrations are between 0.5 – 1.1 IU/mL for 1 mg/kg every 12 hours, and 1.0 – 2.0 IU/mL for 1.5 mg/kg every 24 hours.[19] No major bleeding events were identified in previous studies. [12,14] Additionally, evaluation of anti-Xa adjusted dalteparin dosing found no difference in transfusion requirements.[17] Other evaluations of enoxaparin have found few minor bleeding events such as hematoma following total hip arthroplasty, ecchymosis, hematuria, and epistaxis.[10,20] Based on these previous pharmacokinetic evaluations, patients enrolled in the proposed study would achieve a steady state peak between 0.3 – 0.5 IU/mL and a steady state trough between 0.1 – 0.3 IU/mL. Maintenance of said anti-levels should prevent major bleeding events. Additionally, exclusion of patients with poor renal function, defined as a Cockcroft-Gault calculated creatinine clearance < 30 mL/min will reduce the risk of bleeding events due to reduced drug elimination.

Table 1. Previous pharmacokinetic analyses of enoxaparin.

Trauma Population	Cmax (IU/mL)	Trough (IU/mL)	Half-life (hours)	AUC_{0-12} (IU/L per hour)	Vd (mL/kg)
Non-Edematous*[11] (30 q12h; n = 11)	0.27 (0.19-0.59)	-	1.67 (0.64-3.92)	1.57 (0.91-3.83)	45.8 (28.9-76.4)
Edematous*[11] (30 q12h; n = 10)	0.12 (0.07-0.34)	-	0.68 (0.31-1.97)	0.63 (0.34-2.18)	43.9 (31.2-68.6)
Rutherford[12] (40 mg q24h; n = 17)	0.195±0.088	0.044±0.043	-	-	-
Robinson[14] (40 mg q24h; n = 20)	0.13	-	-	-	-
Robinson[14] (30 mg q12h; n = 30)	0.15	-	-	-	-
Robinson[14] (40 mg q12h; n = 40)	0.33	-	-	-	-
Robinson[14] (1 mg/kg q24h; n = 19)	0.40	-	-	-	-

Study Justification

Ideal enoxaparin dose for VTE prevention in high-risk trauma patients is unknown. Predictors and explanations for low anti-Xa are also unknown. With emerging evidence demonstrating around 50% of trough anti-Xa concentrations are subtherapeutic and associated with increased VTE risk, the purpose of this study is to compare AT-III serum concentrations as a predictor of low anti-Xa. Secondly, the study will compare two enoxaparin dosing. Ultimately, this information can be used to develop an optimum protocol for patient-specific enoxaparin dosing for VTE prevention to improve patient outcomes.

METHODS

Study design

This is an investigator-initiated, single-center, prospective, non-blinded, randomized controlled trial. Multi-system trauma patients between 18-80 years old admitted to the University of Cincinnati Medical Center (UCMC), an urban American College of Surgeons-verified Level 1 trauma center will be identified by the Trauma Surgery team. The trauma team will inform study personnel of these patients once enoxaparin is initiated. These patients will be screened for inclusion in the study. Patients who meet inclusion criteria will be administered informed consent by study personnel in their rooms. Patients in the surgical intensive care unit (SICU) and on the surgical floor are eligible for enrollment if all other inclusion and exclusion criteria are met. Informed consent will be obtained prior to enrollment. Goal enrollment is 200 patients with 100 patients in the control group and 50 patients in each randomization group.

Research data collection/study procedures

Patients will be screened daily by the trauma team. Research personnel will be alerted to potential patients for enrollment.

Intervention

Serum AT-III and anti-Xa will be drawn eight hours after the third dose of enoxaparin 30 mg q12h. Serum assays after at least the third dose should approximate drug steady state trough concentrations. Patients with a serum anti-Xa ≥ 0.1 IU/mL will remain on enoxaparin 30 mg every 12 hours and will be the control group. Patients with undetectable anti-Xa (intervention groups), defined as a trough anti-Xa < 0.1 IU/mL, will be randomized to receive either:

a. Enoxaparin 40 mg every 12 hours (group 1)
b. Enoxaparin 30 mg every eight hours (group 2)

Subsequent trough anti-Xa levels will be performed eight hours after the third dose. Repeat anti-Xa levels will be drawn eight hours after the third dose of the new regimen(s) (see attached figures) for patients in the treatment arms and eight hours after the sixth dose for those in the control arm. For patients in group 2, anti-Xa levels will be drawn within 30 minutes of the fourth and eight doses. If patients continue to be subtherapeutic, the group 1 dose will be increased to 50 mg every 12 hours, while the group 2 dose will remain at 30 mg every eight hours. Group 2 will not have subsequent dose adjustment, as this regimen has not been previously evaluated. Coordinated AT-III and TEG will be performed with the first anti-Xa assessment and the first repeat assessment in the interventional groups. After the initial assessments, weekly anti-Xa and AT-III will be collected on patients requiring dose adjustment for up to 28 days. If the weekly trough anti-Xa level is ≥ 0.3 IU/mL, the enoxaparin dose will be decreased to the previous dose (i.e., enoxaparin 50 mg every 12 hours would be decreased to 40 mg every 12 hours; enoxaparin 40 mg every 12 hours would be decreased to 30 mg every 12 hours; enoxaparin 30 mg every eight hours would be decreased to 30 mg every 12 hours) with patient remaining in enrolled study group for all outcome analyses.

Randomization

Following informed consent, serum AT-III and anti-Xa values will be assayed per protocol. Patients with an anti-Xa level < 0.1 IU/mL undergo unblinded 1:1 randomization to ensure equal allocation to each intervention group. Randomization will be performed by study personnel. If the standard of care anti-Xa per trauma protocol is not collected or inappropriately drawn/mistimed by nursing or phlebotomy staff, patients will be able to have a repeat standard of care anti-Xa within 24 hours of initial draw for assignment to treatment or control groups for enrollment and outcome analysis (protocol amendment). This practice aligns with the current daily trauma protocol operations.

Data Collection:

Coordinated serum anti-Xa, AT-III, and TEG will be collected as previously described. Time to goal anti-Xa achievement will be collected as previously described. Additional data to be collected include patient sex, age, weight, body mass index (BMI), body surface area (BSA), injury mechanism (blunt vs. penetrating), ISS, abbreviated injury score ([AIS] for head, chest, abdomen, extremity, cervical spine, thoracic spine, and lumbar spine), RAP, admission and highest serum creatinine, admission and lowest creatinine clearance (Cockroft and Gault calculated), admission unit (e.g., ICU; floor), time to enoxaparin initiation, heparin initiation (days and number of doses) prior to enoxaparin therapy, VTE events specified, length of stay (hospital and ICU), 28-day mortality, major and minor bleeding events, overall mortality, interruption of study drug, cumulative fluid balance from admission with each serum assay, total milliliters of transfused fluid to date at each anti-Xa assessment, and milliliters of packed red cells transfused in specified time frame.

Specimen collection

Serum assays will be collected as previous described. In summary, initial AT-III and anti-Xa concentrations will be performed eight hours after the third dose of enoxaparin 30 mg q12h. Repeat anti-Xa assessment will be performed after the third dose of the new enoxaparin regimen, based on patient randomization. Coordinated AT-III and TEG will be performed with the first anti-Xa assessment and the first repeat assessment in the interventional group. After the initial assessments, weekly anti-Xa and AT-III will be collected on patients requiring dose adjustment for up to 28 days. All serum anti-Xa and coordinated AT-III and TEG will be drawn 30 minutes prior to stated dose.

Subjects will have the serum assays drawn by either nursing staff via central catheter access or phlebotomy via peripheral venous access. All labs will be drawn using two 2.7 mL blue top, sodium citrate tubes. One tube is needed for the TEG, while the other is used for the AT-III and anti-Xa.

Potential Benefits
VTE are associated with a high morbidity and mortality. Optimal LMWH dosing has not been established for critically injured patients who have altered pharmacokinetics due to altered volume of distribution and metabolism, variable age and weight, and potential decreases in AT-III. Subtherapeutic serum anti-Xa trough concentration has been associated with increased risk for VTE. This pilot clinical investigation has the potential to revolutionize enoxaparin dosing and VTE prevention through anti-Xa guided dosing. Thorough evaluation of risk factors for reduced anti-Xa may provide a focused assessment of patients requiring anti-Xa assessment and subsequent dose adjustments. Overall, optimal enoxaparin dosing will result in fewer VTE events without increasing bleeding risk with an anti-Xa driven adjustment. Improved patient outcomes, expansion of scientific knowledge, and development of VTE prevention protocols may result.

Potential Risks, Discomforts, and Inconveniences
Level of Risk
VTE risks with inadequate prophylaxis have been previously justified above. Risks of increased enoxaparin doses include major and minor bleeding events. Risks will be mitigated by appropriate exclusion of patients with low body weight and increased serum creatinine / decreased creatinine clearance. Serum assays for risk of bioaccumulation will be performed weekly with subsequent dose reduction. Additionally, patient serum creatinine and creatinine clearance will be assessed daily by the trauma team with appropriate therapy modification should patient's renal function worsen. Patients with a 50% change in serum creatinine or an absolute change in serum creatinine by 1 mg/dL will be removed from the study. If these changes in renal function occur after patient has received initial laboratory assessment (i.e., anti-Xa; AT-III; TEG) will be included in the primary outcome analysis.

Blood volume loss due to serum anti-Xa, TEG, and AT-III assay as described above is minimal (2.7 mL x 2). Patients requiring peripheral vein access for serum assays will be at risk for pain/discomfort, bruising, fainting, and infection from phlebotomy sites.

Data Safety Monitoring Plan
Collected data will be screened for adverse events. Jason Schrager, MD will act as medical monitor and review collected data and all adverse events to ensure patient safety.

Data Analysis
Primary Endpoints
1. Initial AT-III activity between the control group and the intervention group.
2. Proportion of patients reaching goal anti-Xa between group 1 and group 2 overall, at first repeat assessment, and at second repeat assessment.
3. Median time to achievement of goal anti-Xa between group 1 and group 2.

Secondary Endpoints
1. Patient outcomes to be compared between control and intervention groups including all VTE events (i.e., pulmonary embolism; upper extremity deep venous thromboembolism [DVT]; proximal lower extremity DVT; distal lower extremity DVT), major bleeding (i.e., hemoglobin decrease of ≥ 2 g/dL in a 24 hour period requiring ≥ 2 units of packed red blood cells while on enoxaparin; worsened or new intracranial hemorrhage while on enoxaparin; repeat surgical intervention due to hemorrhage while on enoxaparin), minor bleeding (minor gastrointestinal bleeding [coffee ground emesis with or without < 2 units packed red cell transfusion needed while on enoxaparin]; interruption of study drug by trauma team; other overt bleeding not characterized a major while on enoxaparin), total transfusion requirements after 48 hours until discharge or admission day 28.
2. Proportion of patients with enoxaparin bioaccumulation (defined as an anti-Xa ≥ 0.3 IU/mL at any assay) between group 1 and 2.
3. Risk factor determination for low anti-Xa.

Statistical analyses will be performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC). An intention-to-treat model will be used for data analysis. Patients excluded due to change in renal function will be included in the primary outcome analysis, but not patient outcome analyses for VTE and bleeding outcomes. Nominal data will be reported using frequencies of occurrence and proportions as appropriate. Continuous data will be reported using means and standard deviations or medians and ranged as appropriate per distribution. Hypothesis testing for nominal data will be performed using the Fisher's exact test or chi square test as required based on sample size. Continuous data will be compared using student's t-test/ANOVA or rank sum/Kruskal-Wallis ANOVA for normally distributed and non-normally distributed data, respectively. A p-value < 0.05 will designate statistical significance. Time-to-event analyses will be compared as appropriate and presented as Kaplan-Meier curves. Multivariate logistic regression will be performed for low anti-Xa risk determination. All values with a p-value < 0.2 will be included in the model. Serum AT-III, weight, and age will be forced into the model, regardless of p-value.

A total of 200 patients will be enrolled. Assuming that 50% of patients will have an undetectable anti-Xa on enoxaparin 30 mg every 12 hours, we hypothesize the intervention group will have an absolute reduction in AT-III activity of 10% compared to the control group if the control group has a mean AT-III activity of 80% with a standard deviation of 25%. Secondarily, we hypothesize that there will be an absolute difference of 27% in the proportion of patients who achieve goal anti-Xa between group 1 and group 2, assuming 50% of group 1 achieves goal. To achieve an 80% power with an alpha of 0.05 for both outcomes, goal enrollment is 200 patients (table 2).

Table 2. Power analysis for each outcome

AT-III activity difference between control and intervention		
Absolute difference in means	*Standard Deviation*	*Sample Size*
10%	25%	200
10%	30%	286
10%	10%	34
20%	30%	74
20%	10%	12
Anti-Xa ≥ 0.1 IU/mL attainment between group 1 and group 2		
Group 1 Proportion	*Group 2 Proportion*	*Sample Size*
50%	77%	100
50%	75%	116
60%	80%	164
80%	90%	398
70%	80%	588

VTE reduction between study groups			
Estimate Source	Control Proportion	Intervention Proportion	Sample Size
Malinoski[15]	37%	11%	98
Droege[17]	14.5%	5.5%	390
2013 UCMC Trauma Registry VTE	5.5%	2.5%	1468
2013 UCMC Trauma Registry VTE	5.5%	4.5%	6576

Data storage and confidentiality (include sample storage if applicable)

A single, central, electronic database will be constructed using Microsoft Excel® for storing all study-related data (attached). The database will be password protected such that only authorized study personnel can access the data. Data will be maintained in a confidential manner with regular reminders of the need for confidentiality provided from the senior investigator. A single subject log will be kept for matching patient study number, initials, medical record number, and admission date (attached). Once assigned to the log, patients will only be evaluated using their de-identified, study number. Data entered into the electronic database will be de-identified.

Once the study has been completed, the electronic database will be maintained in a locked office, per the IRB specifications. Only study personnel will have access to the data. Once the IRB-approved time has elapsed, all materials will be destroyed.

Study Population
Patients admitted to the UCMC trauma service are eligible for enrollment.

Inclusion Criteria

a. Patients with an anticipated length of stay of at least 72 hours
b. High-risk patients initiated on enoxaparin 30 mg every 12 hours per the existing VTE prophylaxis protocol
    a. High-risk is defined as patients with a risk assessment profile (RAP) ≥ 5.[19]
    b. Trauma team VTE prophylaxis protocol contraindications to chemical prophylaxis include
        i. Intracranial bleeding (e.g., chemical prophylaxis contraindicated within 24 hours of documented stable head computed tomography [CT]),
        ii. Incomplete spinal cord injury with hematoma within 24 hours post-injury
        iii. Ongoing hemorrhage
        iv. Uncorrected coagulopathy
        v. ≥ grade IV liver or spleen injury
        vi. Intraocular injuries.
c. Age 18 – 80 years old

Exclusion Criteria

a. Renal dysfunction (creatinine clearance < 30 mL/min or patients on continuous renal replacement therapy)
b. Weight < 50 kg or > 150 kg
c. Platelet count < 50 x 10^3
d. Allergy to heparin or low molecular weight heparins
e. Patients on therapeutic anticoagulation at admission or requiring it within 24 hours of admission
f. Isolated intracranial hemorrhage
g. Known hyperbilirubinemia (defined as serum bilirubin > 6.6 mg/dL; interferes with the anti-Xa chromogenic assay)
h. Patients with a RAP score ≥ 5 without enoxaparin initiated within 72 hours of admission
i. Pregnancy
j. Incarceration

Patients with a 50% change in serum creatinine or an absolute change in serum creatinine by 1 mg/dL after randomization will be removed from the study. If these changes in renal function occur after patient has received initial laboratory assessment (i.e., anti-Xa; AT-III; TEG), the patient will be included in the primary outcome analysis per intention-to-treat design.

Consenting process and plan
Patients will be identified as previously described per trauma service. Permission to consent per the trauma team attending will be obtained prior to administration of consent. Patients initiated on enoxaparin 30 mg every twelve hours prior per the trauma protocol who meet inclusion and exclusion criteria will be eligible for consent. Study personnel will administer in the patient's room. Informed consent will be obtained prior to first serum laboratory assay. The trauma team should alert research personnel as soon as possible for administration of informed consent. Patients will be able to be consented and enrolled up to four hours prior to the first serum laboratory assay. At-risk or vulnerable patients unable to give consent will have next of kin consented. Investigators will be available seven days a week and will

continue correspondence with subjects throughout the study and until hospital discharge (see “Informed Consent” form).

Compensation
Patients will not receive any direct compensation for research involvement.

Subject costs
There are no additional costs to subjects.

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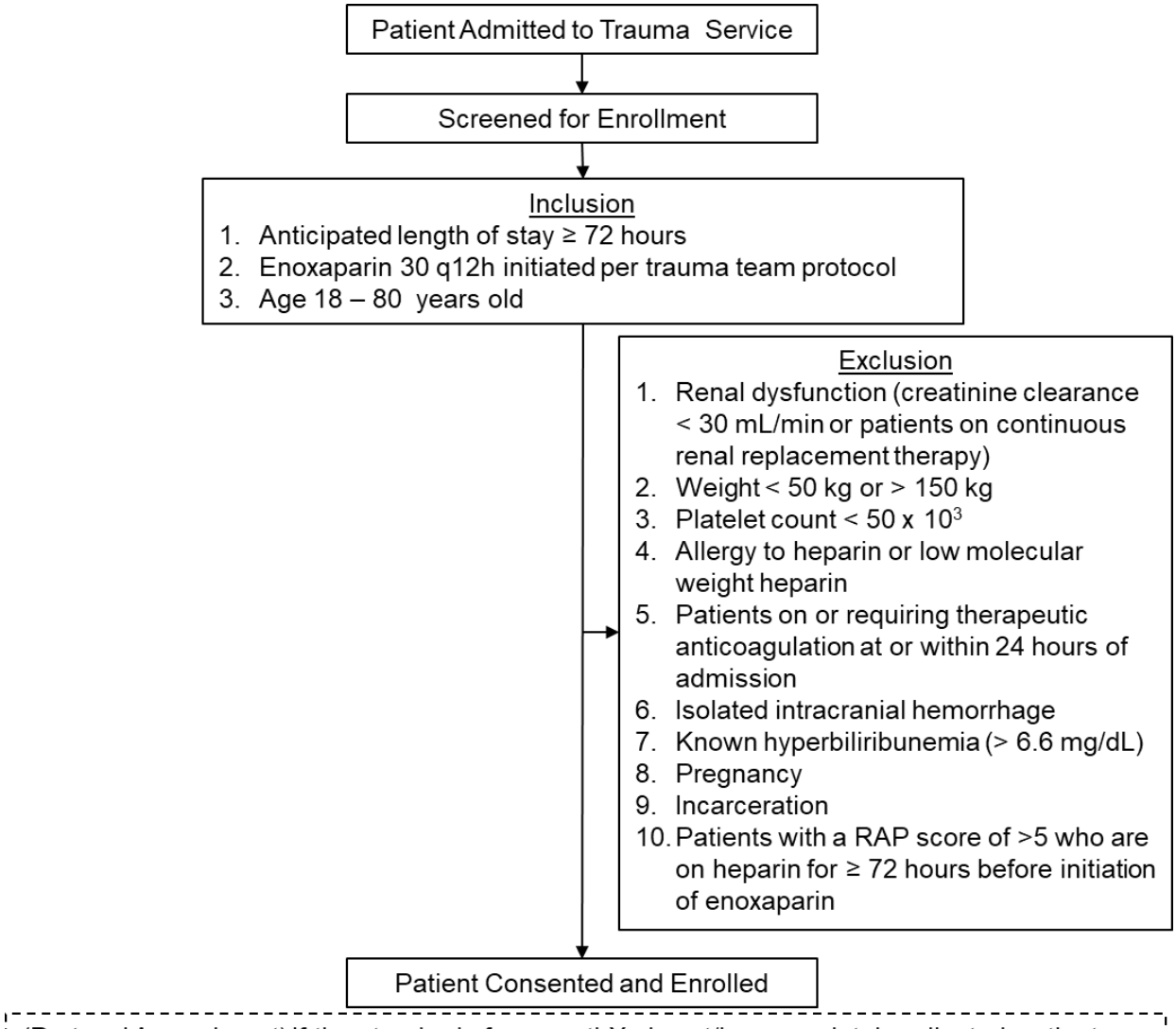
STUDY ENROLLMENT FIGURES



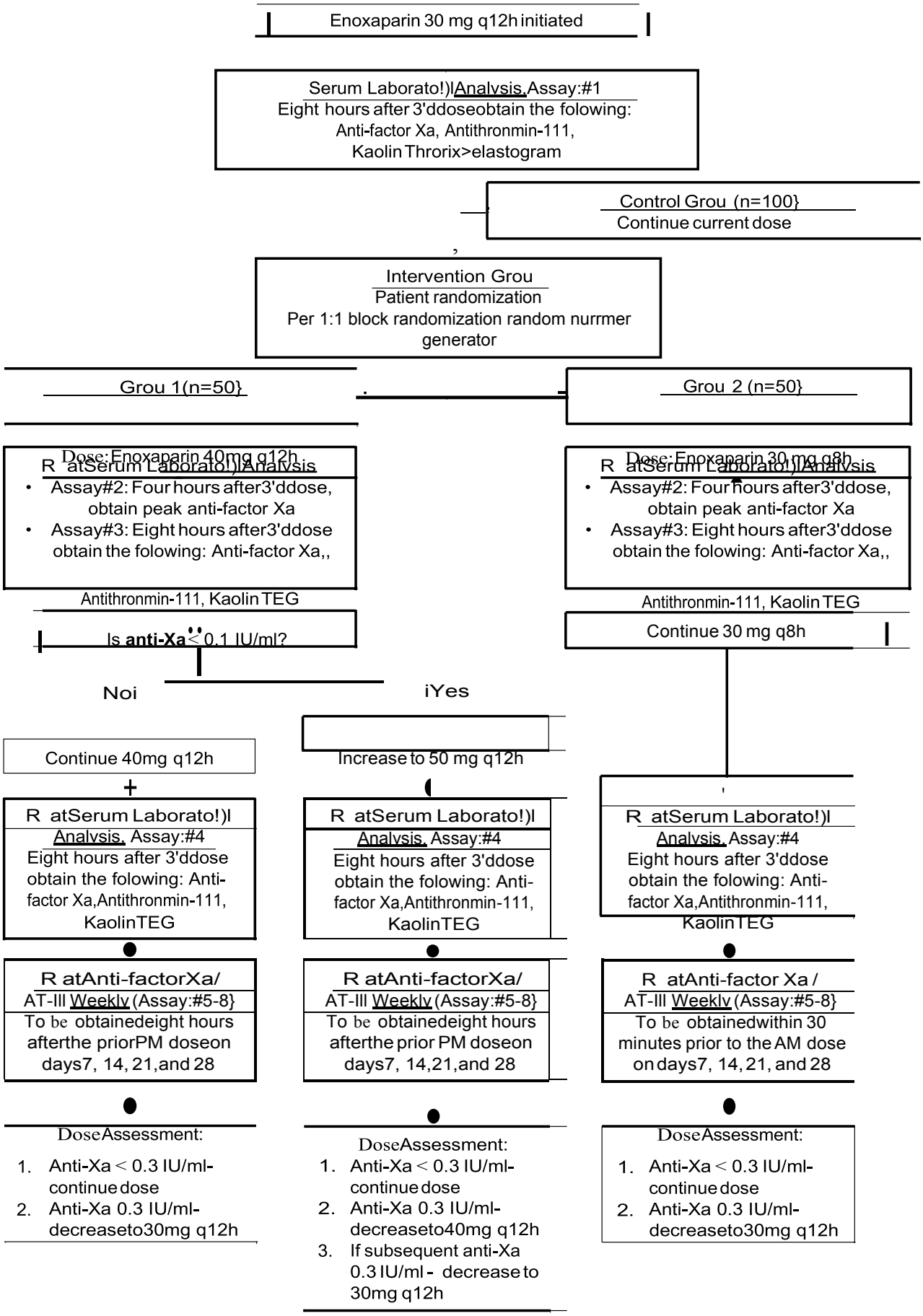
(Protocol Amendment) If the standard of care anti-Xa is not/inappropriately collected, patient can have repeat within 24 hours and remain in the study.
(Protocol Amendment) patients will be able to be consented up to 4 hours prior to first assay.

Event Definitions:

- VTE: Pulmonary embolism, DVT (upper and lower extremity)
- Major Bleeding: hemoglobin decrease of ≥ 2 g/dL in a 24 hour period requiring ≥ 2 units of packed red blood cells while on enoxaparin; worsened or new intracranial hemorrhage while on enoxaparin; repeat surgical intervention due to hemorrhage while on enoxaparin
- Minor Bleeding: minor gastrointestinal bleeding [coffee ground emesis with or without < 2 units packed red cell transfusion needed while on enoxaparin]; interruption of study drug by trauma team; other overt bleeding not characterized a major while on enoxaparin

Dose Adjustments/Removal from Study:

- Dose adjust: trough anti-Xa ≥ 0.3 IU/mL (see next page)
- Remove from study: 50% change in serum creatinine ; absolute change in serum creatinine of 1 mg/dL; new or worsening intracranial hemorrhage while on study dose


Enoxaparin 30 mg q12h initiated
Serum Laborato!)lAnalysis,Assay:#1
Eight hours after 3'ddoseobtain the folowing:
Anti-factor Xa, Antithronmin-111,
Kaolin Throrix>elastogram
Control Grou (n=100}
Continue current dose
Intervention Grou
Patient randomization
Per 1:1 block randomization random nurrmer generator
Grou 1(n=50}
Grou 2 (n=50}
Dose: Enoxaparin 40mg q12h
R atSerum Laborato!)lAnalysis
• Assay#2: Four hours after3'ddose, obtain peak anti-factor Xa
• Assay#3: Eight hours after3'ddose obtain the folowing: Anti-factor Xa,,
Antithronmin-111, Kaolin TEG
Dose: Enoxaparin 30 mg q8h
R atSerum Laborato!)lAnalysis
• Assay#2: Four hours after3'ddose, obtain peak anti-factor Xa
• Assay#3: Eight hours after3'ddose obtain the folowing: Anti-factor Xa,,
Antithronmin-111, Kaolin TEG
Is anti-Xa < 0.1 IU/ml?
Continue 30 mg q8h
Noi
iYes
Continue 40mg q12h
+
Increase to 50 mg q12h
R atSerum Laborato!)l Analysis, Assay:#4
Eight hours after 3'ddose obtain the folowing: Anti-factor Xa,Antithronmin-111, KaolinTEG
R atSerum Laborato!)l Analysis, Assay:#4
Eight hours after 3'ddose obtain the folowing: Anti-factor Xa,Antithronmin-111, KaolinTEG
R atSerum Laborato!)l Analysis, Assay:#4
Eight hours after 3'ddose obtain the folowing: Anti-factor Xa,Antithronmin-111, KaolinTEG
R atAnti-factorXa/ AT-III Weekly (Assay:#5-8}
To be obtainedeight hours afterthe priorPM doseon days7, 14, 21,and 28
R atAnti-factorXa/ AT-III Weekly (Assay:#5-8}
To be obtainedeight hours afterthe prior PM doseon days7, 14,21,and 28
R atAnti-factor Xa / AT-III Weekly (Assay:#5-8}
To be obtainedwithin 30 minutes prior to the AM dose on days7, 14, 21, and 28
DoseAssessment:
1. Anti-Xa < 0.3 IU/ml- continue dose
2. Anti-Xa 0.3 IU/ml- decreaseto30mg q12h
DoseAssessment:
1. Anti-Xa < 0.3 IU/ml- continue dose
2. Anti-Xa 0.3 IU/ml- decreaseto40mg q12h
3. If subsequent anti-Xa 0.3 IU/ml - decrease to 30mg q12h
DoseAssessment:
1. Anti-Xa < 0.3 IU/ml- continue dose
2. Anti-Xa 0.3 IU/ml- decreaseto30mg q12h

INFORMED CONSENT FORM

UNIVERSITY OF CINCINNATI - Medical
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Evaluation of Venous Thromboembolism Prevention in High-Risk Trauma Patients: A Prospective, Randomized Trial of Standard Enoxaparin Versus Two Anti-Xa Adjusted Dosing Strategies

UC IRB Study #: 2014-3627 **Sponsor Name:** US Air Force

Investigator Information:

Molly Droege	513-584-2126
Principal Investigator Name	Telephone Number 24 hr Emergency Contact

Subject Name:_____ Date of Birth:____/____/____

INTRODUCTION:

A biomedical or health-related research study is performed to answer specific questions about a disease.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study. The informed consent document is a written summary of this information. Be sure to ask questions while you read this consent document and ask questions if there is anything that you do not understand.

Your participation in this research study is entirely voluntary.

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

The researcher and sponsor of this study do not promise that you will receive any benefits from this study.

If you are acting as a representative to give consent for another person to participate in this study, “you” throughout this consent form refers to that individual.

The obligation of a representative is to try to determine what the individual would do if competent, or if the subject's wishes cannot be determined, what the representative thinks is in the person's best interest. If possible, an attempt should be made to obtain

permission from the individual. Some persons may resist participating in a research protocol that has been approved by their representatives. Under no circumstances may individuals be forced to participate.

WHY IS THIS RESEARCH BEING DONE?

There are two reasons this research is being done.

1.) To find blood markers that may explain why some patients have low levels of the drug enoxaparin. Enoxaparin is used to stop blood clots from being made. Blood clots are usually formed in the legs and the lungs. If a blood clot occurs in the lungs, it can be life threatening. People with major injuries are at high risk for blood clots.
2.) To learn the best dose of the medicine enoxaparin in patients with injuries.

Enoxaparin is approved by the Food and Drug Administration (FDA) for the prevention of blood clots. Enoxaparin is the accepted drug for prevention in trauma patients by many physician groups including the United States Air Force.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because, you are at least 18 years old and not more than 80 years of age, have a traumatic injury and have a high risk of forming a blood clot.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for up to four (4) weeks or until you are discharged from the hospital, whichever comes first.

The researcher may decide to take you off this research study at any time. The treatment team may also decide to take your off this research at any time. If you have side effects that could be from the study medications, you will be taken out of the study. If there are any changes in your condition that would increase your risk of bleeding, the study medication will be stopped temporarily or permanently and you may be removed from the study.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

You may be contacted in the future by representatives of the University of Cincinnati who are interested in asking you survey questions about your participation in this research study. If you choose to participate in the survey, your responses will be used for quality assurance purposes only.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the United States Air Force.

The study is directed by Molly Droege, PharmD, the researcher at the University of Cincinnati Medical Center. Medical supervision for the study is provided by Krishna Athota, MD.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 200 people will take part in this study at the University of Cincinnati Medical Center.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

You will be receiving 30 mg of enoxaparin twice daily as part of your clinical care.

If you choose to participate in the study, you will have 5.4 mL of blood (a little over a teaspoon) drawn before receiving your fourth (4th) standard of care dose of enoxaparin to have three blood tests run.

1. Antithombin-III (AT-III) – is naturally in your body. Enoxaparin works with it to stop clots from forming. Measuring AT-III ensures the drug has the ability to work in your body.
2. Anti-activated factor Xa (anti-Xa) – measures how much enoxaparin is in your body.
3. Thromboelastography (TEG) – measures how well your body forms clots.

These blood labs will allow the investigators to determine what affects enoxaparin and how well enoxaparin stops clots from forming. You may benefit from this extra monitoring.

If your anti-Xa level is normal, you will continue on the current dose of enoxaparin. No additional blood tests will be taken.

If your anti-Xa level is low, you will receive one of two following investigational doses of enoxaparin. These doses are higher than the FDA approved dose. The doses are:

1. Enoxaparin 40 mg injected under the skin twice a day
2. Enoxaparin 30 mg injected under the skin three times a day

Which dose you receive will be determined completely by chance. You will have an equal chance of being placed in either group. This dose adjustment may benefit you by decreasing your risk of blood clot.

Four hours after receiving the third investigational dose, 2.7 mL of blood will be drawn to run an anti-Xa test. This will tell the investigators how much enoxaparin is in your blood when the drug is at its highest amount.

Before the fourth investigational dose, you will have 5.4 mL (a little over a teaspoon) of blood drawn to run the three tests again. The three tests are the AT-III, anti-Xa, and TEG. These tests may benefit you because they will tell the investigators how well the drug is preventing blood clots. If your anti-Xa level is still low and you are in the group receiving enoxaparin 40 mg twice a day, your dose will be increased to 50 mg twice a day. Otherwise your dosage will remain the same. If your anti-Xa level is too high, your dose will be decreased to 30 mg twice a day. This may benefit you by preventing too much drug from getting in your blood.

Before the fourth adjusted dose for the group receiving 50 mg twice a day, or the eighth investigational dose for the 30 mg every eight (8) hours group, you will have 5.4 mL of blood drawn again to run the three tests. The three tests are the AT-III, anti-Xa, and TEG.

Additional blood (2.7 mL each time) will be drawn to test Anti-Xa levels on days seven (7), fourteen (14), twenty-one (21), and twenty-eight (28) if you are still in the hospital and are in one of the groups receiving the investigational doses.

The expected maximum amount of blood that will be drawn if you are in one of the investigational groups for the entire 28 days is 29.7 mL or about two tablespoons.
If at any time your anti-Xa level gets too high, your dose will be decreased back to the previous dose. If at any time the trauma team believes you are having abnormal bleeding, a dose will not be given until it is determined to be safe or bleeding has stopped.

If you decide to withdraw from the study at any time, you will resume the standard care enoxaparin dosage. The standard dose is 30 mg twice per day. Depending on when you withdraw from the study, the team may draw an anti-Xa and adjust your dose to 40 mg twice per day. This is the current routine care for trauma patients at the University of Cincinnati Medical Center.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

There may be unknown or unforeseen risks associated with study participation.

Common side effects of enoxaparin:

- Low red blood cell and platelet counts
- Redness, irritation, and bleeding at the injection site
- Minor bleeding such as bruising or from existing cuts or injuries
- Feeling light-headed, dizzy, or fainting
- Tiredness
- Allergic reaction
- Skin rash or hives
- Nose or gum bleeding
- Red or tarry stools

- Red or dark brown urine

There may be risks of drawing blood (venipuncture). Risks of having your blood drawn include faintness, inflammation of the vein, pain, bruising, bleeding at the site of the puncture and, rarely, infection.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, you will have additional monitoring outside normal care that may benefit you. Specifically, the blood samples being collected will determine how well enoxaparin is preventing blood clots. Additionally, it is possible that adjusted enoxaparin dosing may decrease the risk of clot formation and blood clot-related death. The investigator evaluations are over and above the standard of care. Information learned from this research study may benefit you while you are enrolled in the study and benefit other patients with injury in the future.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you can continue with the usual standard for clot formation prevention. The physicians on the trauma service will continue to prescribe enoxaparin or other medications and devices for the prevention of clot. This is the trauma service standard of care for patients at risk for clot formation.

WHAT IS THE CLINICAL TRIALS REGISTRY?

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed and dated consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

There are no additional costs to you or your insurance for participation in this study. Any study costs for blood samples, doses given above 30 mg twice daily, or other study-related tests will be paid for by the study funding.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid to participate in this study

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. Any illness or injury that directly occurs from the study will be reviewed by the University of Cincinnati. The University of Cincinnati will decide on a case by case basis if the harm was due to research and reimburse you for your out of pocket health care expenses

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research records related to this study. Agents of the United States Food and Drug Administration (FDA), The US Air Force, the University of Cincinnati, the monitor, the auditor, the Institutional Review Board (IRB), and other regulatory authority(ies) will be granted direct access to your original medical and research records for verification of clinical trial (research study) procedures or study data without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing this consent form, you or your legally authorized representative are authorizing such access. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

Authorization to Use and Disclose Health Information

A federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you. You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you.

If you sign this informed consent form, you are giving permission for the use and

disclosure of your health information for purposes of this research study. You do not have to give this permission. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form. However, if you do not sign this form, you will not be able to participate in the study.

Who Will Use and Disclose My Health Information? The study doctor and research staff (the study team) may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication without your permission.

What Health Information will be Used and Disclosed? The study team will record your medical history, the treatment you receive, and the results of examinations and tests done during the study on study forms. The study team will send the completed study forms to the study sponsor. Representatives from the groups identified below may need to look at your medical records to make sure that the information on the studyforms is correct or that the study was conducted properly. Your medical records may include other health information about you and may include documents that directly identify you. Reviews like that will take place at the study center or where the medical records are stored and can take place after the study is over.

Who Will Receive My Health Information? Your study information or medical records (as described above) or both may be shared with the following people or groups:

- The study sponsor or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other study centers
- UC Institutional Review Board and any other committees responsible for overseeing the research
- Staff of the UC Human Research Protection Program
- UC Health employees providing service or care to you
- Federal and State agencies, such as the U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), the National Institutes of Health (NIH), and other US and non-US government bodies that oversee or review research

Will My Information be Protected by the Privacy Rule After it is Disclosed to Others?

UC Health are required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form and could disclose it to others. The sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the sponsor may reanalyze the study data at a later date or combine your information with information from other

studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs or diseases or to help design better studies in the future. When using your information in these ways, the sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services.

What Happens if I Leave the Study Early? If you stop participating in the study early for any reason, the study team will tell the sponsor why. If the study team asks you to come to any more study visits and you agree, the study team will send the sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire? This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over and a review of your medical records may also take place after the study is over.

May I Take Back My Authorization? You have the right to take back (revoke) your Authorization at any time by writing to the person in charge of this research study whose information is listed on the front of this form. If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already-collected information if that is necessary for the reliability of the study. The sponsor can also still keep and use any information that it has already received. If you revoke your Authorization, you can no longer continue to participate in the study.

May I Look At My Study Information? You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher Molly Droege at 513-584-2126.

Please call the University of Cincinnati Institutional Review Board at 513-558-5259 (Monday – Friday 8 am to 5 pm) if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, or complaints about the research.
- Cannot reach the research team or you want to talk to someone else.

To report complaints or concerns to an independent agency in an anonymous and confidential manner, please call the Research Compliance Hotline at 1-800-889-1547.

UNIVERSITY OF CINCINNATI - Medical
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Evaluation of Venous Thromboembolism Prevention in High-Risk Trauma Patients: A Prospective, Randomized Trial of Standard Enoxaparin Versus Two Anti-Xa Adjusted Dosing Strategies

UC IRB Study #: 2014-3627 **Sponsor Name:** US Air Force

Investigator Information:

Molly Droege	513-584-2126
Principal Investigator Name	Telephone Number 24 hr Emergency Contact

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. If I do not participate or if I discontinue my participation, I will not lose any benefits or any legal rights. My participation in this research is completely voluntary. I have received (or will receive) a copy of this signed and dated form for my records and future reference. I have been given the information about the use and disclosure of my health information for this research study.

Subject or Legally Authorized Representative or Next of Kin (Printed Name)	Relationship to Subject

Subject or Legally Authorized Representative or Next of Kin (Signature)	Date

PERSON OBTAINING CONSENT
I have read this form to the participant and/or the subject has read this form. An explanation of the research was given and questions from the participant were solicited and answered to the participant's satisfaction. In my judgment, the participant has demonstrated comprehension of the information.

Signature and Title of Person Obtaining	Date

Consent and Identification of Role in the Study

Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

____I **want** the researcher to inform my primary care physician/specialist of my participation in this study.

____I **do not** want the researcher to inform my primary care physician/specialist of my participation in this study.

___I do not have a primary care physician/specialist.

___The researcher is my primary care physician/specialist.

_____

Participant Date