Please indicate if this is a...
New MCT proposal submission

If a revised proposal summarize the changes made to this proposal based on the feedback received:

Study Title
Anti Factor Xa Monitoring of Venous Thromboembolism Prophylaxis in Emergency General Surgery Patients: A prospective multi-center study.

Are you a current member of EAST?
No

Use this area to briefly outline the burden of the problem to be examined.
In the United States, venous thromboembolism (VTE) affects an estimated 300,000 to 600,000 patients each year. Of those, it is estimated 10-30% of patients will die within 30 days (1). Risk factors for VTE include surgery, immobility, obesity, and advanced age. Optimal chemical VTE prophylaxis has been studied extensively in the trauma and orthopedic surgical literature, but there is a significant knowledge gap in optimal dosing strategies of chemical VTE prophylaxis in emergency general surgery patients. Patients with emergency general surgery (EGS) conditions, including those managed non-operatively, are at an above average risk for VTE when compared to their elective surgical counterparts (2). Since the mid-1990s, low dose molecular weight heparin, or enoxaparin, has been shown to be superior to unfractionated heparin for prevention of DVT in trauma patients, and is often used in most surgical specialties (3). Anti-Factor Xa (AFXa) is used as a measurement for enoxaparin activity, and recent literature has shown that standard dosing (30mg BID or 40mg daily) has resulted in sub-prophylactic AFXa levels (4,5) and has been associated with VTE(6). Attempts to personalize chemical VTE prevention have largely been based on body mass index (BMI), but this strategy is not supported pharmacologically and does not improve AFXa levels in obese patients (7). Twice a day dosing has been recommended in the trauma population for decades (3). There is evidence that low AFXa levels have been associated with the development of VTE (4,8), and that an individualized approach to VTE prevention can improve in-range AFXa levels (4).

Briefly review what major published studies exist on the topic of the proposed product.
Single center studies have shown emergency general surgery patients have inadequate enoxaparin prophylaxis with fixed-dose regimens (13). Low Anti-Factor Xa (AFXa) levels have been associated with symptomatic VTE (6). Guidelines in physiologic similar patients (trauma) support higher dosing regimens with a goal anti Xa of 0.2-0.4 IU/mL to prevent venous thromboembolism (7). LMWH is readily absorbed from the subcutaneous tissues as it binds minimally to endothelial cells, and the volume of distribution closely matches blood volume (9). Further, while the recommended enoxaparin dose for abdominal surgical patients is 40mg daily (10), the half-life of enoxaparin is only 7 hours (11). Therefore, once daily dosing may not be adequate from a pharmacokinetic standpoint. Using a pharmacologic-based strategy, our institution developed a novel enoxaparin dosing protocol based on the estimated blood volume (EBV) of individual patients for VTE prophylaxis in trauma patients (7,12). The EBV dosing protocol demonstrated significantly increased attainment of in-range initial AFXa levels (12).

Use this area to briefly outline how this idea is innovative and its anticipated impact.
There are no major published studies focusing exclusively on enoxaparin dosing strategies in emergency general surgery patients. There is published data measuring Anti-Factor Xa (AFXa) levels in trauma, orthopedic, bariatric, colorectal, abdominal surgical oncology, plastic surgery, and thoracic surgical patient, demonstrating fixed dosing regimens do not correlate with adequate AFXa levels (14). Data at our institution has shown that standard 40mg daily dosing of enoxaparin has resulted in mostly sub-prophylactic AFXa (13). Additional preliminary data from our institution has shown that individualized dosing leads to significantly higher in-range anti-Xa levels in the EGS population. Optimizing prophylaxis for acute care surgery patients is imperative to prevent venous thromboembolism in surgical patients.

Describe what & how the proposed MCT will add to the existing body of knowledge & literature.
This study will add additional data to the existing and growing literature regarding optimal dosing of prophylactic enoxaparin in surgical patients. Minimal data is available for optimal enoxaparin dosing in emergency general surgery patients. This MCT will help us assess if we are underdosing our emergency general surgical patients and putting them at higher risk of VTE, which is a major cause of morbidity and mortality. Anti-Xa levels are a surrogate for the important clinical outcome of VTE and a large MCT will also allow secondary analysis of VTE events.

Primary aim
Characterize variation in current enoxaparin dosing protocols for operative and non-operative emergency general surgery patients across the United States.

Secondary aims
Compare enoxaparin dosing protocols with regards to initial in-range anti-factor Xa levels and identify optimal dosing strategy for emergency general surgical patients.

Tertiary aim

Design
Prospective (observational with or without consent requirement)

Inclusion Criteria
1.Patients admitted to the acute care surgery/emergency general surgery service2.Patients 18 years of age and older3.Patients who receive at least three consecutive doses of enoxaparin chemical prophylaxis 4.Patients who have a properly timed Anti-Factor Xa peak level

Exclusion Criteria
1.Patients <18 years of age2.Patients who are not candidates for enoxaparin therapy renal disease, epidural catheter, recent intracranial bleed, active bleeding event precluding use of enoxaparin.3.Patients who are pregnant or are incarcerated.4.Patients with improperly timed Anti Factor Xa peak levels

Please describe, completely but succinctly, how the product will be conducted.
Patients admitted to the emergency general surgery service at each participating institution will be queried for inclusion/exclusion criteria. Those that meet inclusion criteria will receive the standard dose enoxaparin per the institution standard dosing strategy. No changes to dosing strategies will be implemented. Anti-Factor Xa (AFXa) levels will be measured 3-6 hours after three consecutive doses. Patients who received three consecutive doses and properly times AFXa level will be included for analysis. Patients will be stratified by VTE dosing strategy based on individual institution protocols. Analysis will be conducted evaluating in-range AFXa levels, VTE rates, and bleeding complications between groups.

Primary Outcome
The primary outcome will be percentage of patients with in-range initial Anti-Xa peak levels.

Secondary Outcome(s)
Secondary outcomes include rate of VTE, rates of bleeding complications (defined by need for blood transfusion), and rates of in-range Anti-Xa levels after dosing adjustments.

Select the variables to be collected & analyzed:
Baseline Participating Institution Information,Demographics,Baseline Clinical Characteristics,Hospital Course,Treatments & Interventions,Outcomes of Interest

Additional variables:

Outline the data collection plan/tool succinctly
Participating centers will prospectively identify patients from their emergency general surgery census. Patients who receive three consecutive doses of enoxaparin and have an appropriately timed Anti-Xa level will be included in the study. Individual data user agreements will be executed between Medical College of Wisconsin (MCW) and the participating centers. We will establish a secure REDcap database here at MCW. Password protected user accounts for participating centers will be created for data entry. Each center will input their abstracted standardized patient data into REDCap hosted by MCW. Participating centers will be restricted to accessing only their data, in REDCap.

Has IRB approval been obtained at the primary site?
No

Is DUA required for participation in the study?
Yes

Is there a primary statistician assigned to assist the PI w/design & data analysis?
Yes

If no, how was study design/power analysis determined/who will handle analysis once complete?

Include detailed description of the data analysis plan:

Descriptive statistics will be used to examine the proportion of patients both in range (0.2-0.4) and out of range peak AFXa levels and stratified based on dosing strategy. Categorical variables will be expressed as frequency (percent) and compared between groups using chi-square or fishers exact test, as appropriate. Continuous variables will be expressed as mean or median, and ANOVA will be used to compare between two groups. Logistic regression will be performed to compare factors that may influence anti-Xa levels target level attainment including known related variables such as operative intervention and missed doses. There will be a planned sub-group analysis for the same comparison in patients who do not undergo operative intervention. The degree of correlation will be assessed using Spearman's rank correlation coefficient. Analyses will be performed using Stata, and statistical significance will be set at $p < 0.05$.

Include Power Analysis:

Our institutional data demonstrated patients with an EBV based dosing regimen have initial in-range Anti-Xa levels at about 60%, compared to fixed-dosing regimen (once daily Enoxaparin) of 30%. Based on = 0.80, a = 0.05, estimated intraclass correlation of 0.15, and our institution observed differences, we would need 10 institutions with 100 patients enrolled each.

Please note what your enrollment procedure for this study entails:

Institutions will prospectively identify patients admitted to their emergency general surgery service and include patients who receive three consecutive doses of enoxaparin for VTE prophylaxis, with an appropriately timed anti-Xa level after the third dose. Patients will not be consented as we plan to observe outcomes on patients managed according to institutional standards and are not changing practice.

Outline consent procedures here, if applicable:

N/A - This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional protocols for VTE prophylaxis. Thus, waiver of informed consent is requested.

Please indicate what resources are available at the primary study institution:

Presence of a dedicated statistician,Research personnel ,Availability of data collectors

Include a brief listing of key references:

1.Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(4 Suppl):S495-501.2.Yang M, Murphy PB, Allen L, Sela N, Govind S, Leslie K, et al. Venous thromboembolism in emergency general surgery patients: a single-centre retrospective cohort study. Can J Surg. 2020;63(1):E80-e5.3.Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996;335(10):701-7.4.Pannucci CJ, Fleming KI, Bertolaccini CB, Prazak AM, Huang LC, Pickron TB. Assessment of Anti-Factor Xa Levels of Patients Undergoing Colorectal Surgery Given Once-Daily Enoxaparin Prophylaxis: A Clinical Study Examining Enoxaparin Pharmacokinetics. JAMA Surg. 2019;154(8):697-704.5.Berndtson AE, Costantini TW, Lane J, Box K, Coimbra R. If some is good, more is better: An enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. J Trauma Acute Care Surg. 2016;81(6):1095-100.6.Pannucci CJ, Fleming KI, Varghese TK, Jr., Stringham J, Huang LC, Pickron TB, et al. Low anti-Factor Xa level predicts 90-day Symptomatic Venous Thromboembolism in Surgical Patients Receiving Enoxaparin Prophylaxis: A Pooled Analysis of Eight Clinical Trials. Ann Surg. 2020.7.O'Keefe MM, Carver TW, Herrmann DJ, Prom A, Hubbard S, Rein LE, et al. Evaluation of anti-factor Xa concentrations using a body mass index-based enoxaparin dosing protocol for venous thromboembolism prophylaxis in trauma patients. Pharmacotherapy. 2022;42(3):216-23. 8.Verhoeff K, Raffael K, Connell M, Kung JY, Strickland M, Parker A, et al. Relationship between anti-Xa level achieved with prophylactic low-molecular weight heparin and venous thromboembolism in trauma patients: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2022;93(2):e61-e70.9.Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost. 2000;26 Suppl 1:31-8. 10.Sanofi-Aventis. Enoxaparin Full Prescribing Information. Bridgewater, New Jersey: Sanofi-Aventis; 2022.11.Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):15-31. 12.Langenstroer EA, Carver TW, Herrmann DJ, O'Keefe MM, Hubbard S, Holschbach L, et al. Evaluation of a novel blood volume-based enoxaparin dosing guideline for venous thromboembolism prophylaxis in trauma patients. Am J Health Syst Pharm. 2023;80(17):1137- 46. 13.Pokrzywa, Courtney J MD; Biesboer, Elise A MD; Figueroa, Juan MD; Al Tannir, Abdul Hafiz MD; de Moya, Marc MD, FACS; Morris, Rachel S MD, FACS; Murphy, Patrick B MD, MSc, MPH, FACS. Anti-Factor Xa Monitoring of Enoxaparin Thromboembolism Prophylaxis in Emergency General Surgery Patients. Journal of the American College of Surgeons 237(2):p 195-203, August 2023. | DOI: 10.1097/XCS.0000000000000070914.Al Tannir AH, Biesboer EA, Pokrzywa CJ, Figueroa J, Harding E, de Moya MA, Morris RS, Murphy PB. The efficacy of various Enoxaparin dosing regimens in general surgery patients: A systematic review. Surgery. 2023 Aug;174(2):315-323. doi: 10.1016/j.surg.2023.04.032. Epub 2023 May 15. PMID: 37198037.