

# Double-Blind Randomized Clinical Trial to Examine the Pharmacokinetic and Clinical Impacts of Fixed Dose versus Weight-based Enoxaparin Prophylaxis: A Methodologic Description of the Fixed or Variable Enoxaparin (FIVE) Trial

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**Abstract:** Venous thromboembolism is an important patient safety in plastic surgery, and multiple clinical trials in the past 10 years have provided increased understanding of the risks and benefits of venous thromboembolism prevention strategies. This paper provides an exhaustive discussion of the rationale behind and methodology for an in progress randomized double-blind clinical trial in plastic surgery inpatients, in which the 2 study arms are enoxaparin 40 mg twice daily and enoxaparin 0.5 mg/kg twice daily. The trial's primary aims are to: (1) demonstrate whether enoxaparin 0.5 mg/kg twice daily is superior to enoxaparin 40 mg twice daily for the pharmacokinetic endpoint of overanticoagulation (anti-Factor Xa > 0.4 IU/mL) and (2) demonstrate whether enoxaparin 0.5 mg/kg twice daily is not inferior to enoxaparin 40 mg twice daily for the pharmacokinetic endpoint of underanticoagulation (anti-Factor Xa < 0.2 IU/mL). The results of this trial will provide Level I evidence to help guide plastic surgeon's choice of postoperative prophylactic anticoagulation. (*Plast Reconstr Surg Glob Open* 2019;7:e2185; doi: 10.1097/GOX.0000000000002185; Published online 11 April 2019.)

## INTRODUCTION

Venous thromboembolism (VTE), which encompasses deep venous thrombosis and pulmonary embolus (PE), is a critical patient safety issue among hospitalized patients. Approximately 900,000 VTE events occur each year in the United States.<sup>1</sup> VTE is the direct cause of over 250,000 hospitalizations annually in the United States, representing a massive burden to patients and healthcare systems alike. PE is the direct cause of over 100,000 deaths each year, and one-third of these deaths occur after a surgical

procedure.<sup>2-5</sup> The annual cost of VTE to the healthcare system is estimated at 13–27 billion dollars.<sup>6</sup> The US Surgeon General has acknowledged that VTE represents a public health crisis, and prevention of VTE in surgical patients is the key maneuver to minimize VTE-associated morbidity and mortality.<sup>7-10</sup>

Adverse drug events (ADEs) are a research priority for the Department of Health and Human Services, and active efforts exist to target ADEs specific to anticoagulant drugs. Over 218,000 ADEs, which is more than 10% of all events, occur as a direct result of anticoagulant medications in the United States each year. The overwhelming majority of these ADEs are bleeding-related events.<sup>11</sup> ADEs are particularly important among surgical patients who receive anticoagulants, known as chemical prophylaxis, to minimize postoperative VTE risk. Studies across the spectrum of surgical patients have shown that

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chemical prophylaxis reduces VTE risk, often by 50% or more, after surgery.<sup>12–15</sup> However, chemical prophylaxis also increases the risk of postoperative bleeding events that require return to the operating room, transfusion, and/or cessation of chemical prophylaxis with resultant increase in VTE risk.<sup>15–21</sup> In rare cases, postoperative bleeding ADEs can be fatal.

Surgeons often provide suboptimal doses of chemical prophylaxis, delay chemical prophylaxis initiation, or avoid chemical prophylaxis altogether in an attempt to minimize postoperative bleeding.<sup>22–26</sup> Surgeons are less likely to provide chemical prophylaxis after large operations due to risk for ADEs and bleeding—this is troublesome because larger and longer operations carry increased risk for VTE.<sup>27</sup> ADEs related to VTE chemical prophylaxis are unique because they occur due to a prevention strategy (eg, in a patient without disease), as opposed to a treatment strategy.

This paper provides a discussion of the rationale behind and methodology for an in progress randomized double-blind clinical trial in plastic surgery inpatients, whose primary aims are to: (1) demonstrate whether enoxaparin 0.5 mg/kg twice daily is superior to enoxaparin 40 mg twice daily for the pharmacokinetic endpoint of overanticoagulation [anti-Factor Xa (aFXa) > 0.4 IU/mL] and (2) demonstrate whether enoxaparin 0.5 mg/kg twice daily is not inferior to enoxaparin 40 mg twice daily for the pharmacokinetic endpoint of underanticoagulation (aFXa < 0.2 IU/mL). The results of this trial will provide Level I evidence to help guide plastic surgeon's choice of postoperative prophylactic anticoagulation.

### Relevant Preliminary Data

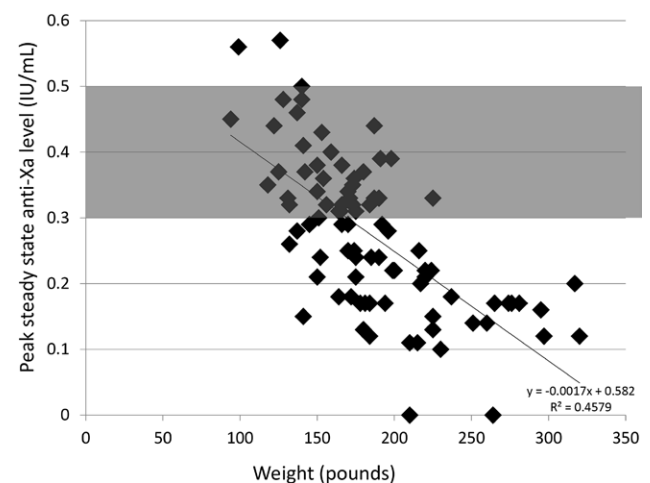
aFXa levels are a marker of enoxaparin activity and can guide enoxaparin administration.<sup>28–41</sup> Peak aFXa level drawn at 4 hours after the third dose is the most reported measure of safety and effectiveness.<sup>29</sup> A peak range of 0.2–0.4 IU/mL for twice daily dosing has been reported as safe and effective for many surgical populations.<sup>29–31,41–45</sup> For once daily dosed enoxaparin, a goal peak range of 0.3–0.5 IU/mL has been reported.<sup>32</sup> Trough levels drawn 11.5–12 hours after a steady-state dose are utilized for the evaluation of impaired enoxaparin clearance.<sup>34</sup> Troughs are also reported as the endpoint in prophylactic enoxaparin trials for trauma and orthopedic surgery patients. In these studies, a low trough is defined as less than 0.1 IU/mL, and a goal trough range is 0.1–0.2 IU/mL.<sup>35–38</sup>

Trial #1 (NCT02411292, March 2015–March 2016) recruited 94 plastic and reconstructive surgery patients who received enoxaparin 40 mg once per day. Steady-state peak aFXa levels showed that less than 50% of patients were adequately dosed using this standard regimen of 40 mg/d (Fig. 1). Most importantly, patients who were underanticoagulated were significantly more likely to have 90-day symptomatic VTE when compared to adequately dosed patients (10.2% versus 0%,  $P = 0.041$ ) (Fig. 2).<sup>32</sup> This trial demonstrated that underanticoagulation is common and is associated with downstream adverse VTE events.

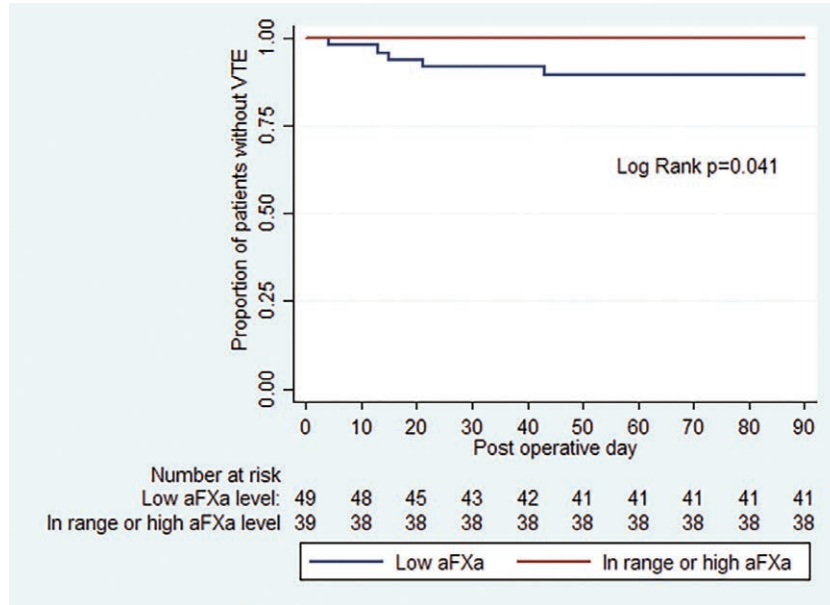
Our subsequent trial (NCT02687204, March 2016–March 2017) enrolled 118 plastic and reconstructive surgery patients who received enoxaparin 40 mg twice daily to examine the impact of increased enoxaparin dose frequency.<sup>42</sup> 27.8% of patients had high peak aFXa levels (>0.4 IU/mL), and this included 11.3% of the overall group with inadvertent therapeutic anticoagulation (peak aFXa > 0.5 IU/mL) from a prophylactic dose. 60.2% of patients had in range peak aFXa levels (0.2–0.4 IU/mL), and 9.2% of patients had low peak aFXa levels (<0.2 IU/mL). All patients who achieved therapeutic anticoagulation (peak aFXa > 0.5 IU/mL) had body weights less than 90 kg (Fig. 3).

Patients who receive enoxaparin 40 mg twice daily are significantly less likely experience underanticoagulation than patients who receive enoxaparin 40 mg per day (9.6% versus 53.4%,  $P < 0.001$ ) (Figs. 1 and 3).<sup>46</sup> However, the more aggressive dosing regimen comes with a cost: 27.8% of patients had high aFXa levels (>0.4 IU/mL), and 11.3% of all patients had inadvertent therapeutic anticoagulation (aFXa > 0.5 IU/mL). Patients who received enoxaparin 40 mg twice daily were significantly less likely to have 90-day VTE events (0% versus 5.3%,  $P = 0.012$ ) but had substantial increase in clinically relevant bleeding that manifested as an over 2-fold increase in events (6.8% versus 3.2%,  $P = 0.25$ ).<sup>46</sup> The more aggressive strategy prevents VTE, but comes with the cost of substantial increase in ADEs.

We modeled the impact of weight-based twice daily enoxaparin dosing by transforming the fixed 40 mg twice daily dose into a weight-based dose for 115 patients with appropriately timed laboratory draws. Patient weights ranged from 50–185.1 kg, resulting in a weight-based enoxaparin dose of 0.22–0.79 mg/kg twice daily.<sup>46</sup> Figure 4 shows that enoxaparin 0.5 mg/kg twice daily may allow an increased proportion of patients to have in range aFXa levels while minimizing risk for both low (<0.20 IU/mL) and high (>0.40 IU/mL) peak aFXa levels. This could



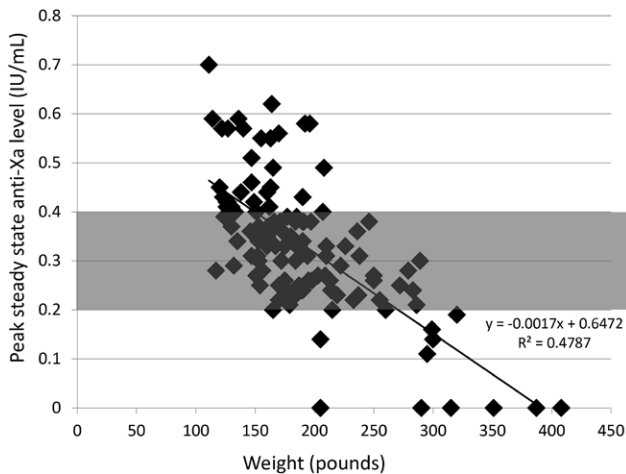
**Fig. 1.** Peak aFXa stratified by weight among patients who received enoxaparin 40 mg once daily. Gray box represents in range peak aFXa level. Reprinted with permission from *Plast Reconstr Surg.* 2017;139:1009–1020.



**Fig. 2.** Survival time analysis showing a significant association between low peak aFXa and 90-day VTE in plastic surgery patients. Reprinted with permission from *Plast Reconstr Surg.* 2017;139:1009–1020.

substantially decrease both bleeding-related ADEs related to high aFXa levels and VTE events related to low aFXa levels.

Our preliminary data support that a patient-centric, weight-based approach to enoxaparin prophylaxis may optimize both the risks and benefits of chemical prophylaxis. Thus, the proposed RCT may challenge current dogma that a “one size fits all” approach using a standard unadjusted enoxaparin dose is appropriate for all surgical patients. Data from a randomized double-blind clinical trial could provide Level I evidence that examined whether weight-based enoxaparin dosing could optimize both the effectiveness and safety of this chemical prophylaxis strategy.



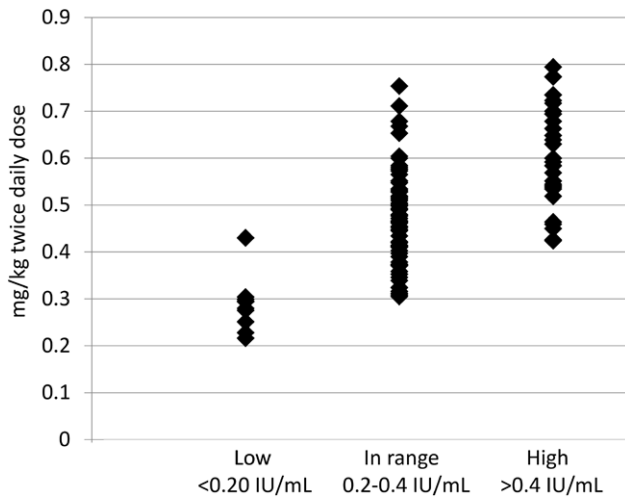
**Fig. 3.** Peak aFXa stratified by weight among patients who received enoxaparin 40 mg twice daily. Gray box represents in range peak aFXa level. Reprinted with permission from *Plast Reconstr Surg.* 2018;141:1580–1590.

## METHODS

The trial has IRB approval at the University of Utah (IRB 00100416, initial approval May 15, 2017, continuing review approved April 3, 2018). The study was registered on clinicaltrials.gov (NCT03212365) before enrollment of patient 1 on July 1, 2017, with the official title “Minimization of Bleeding Related Adverse Drug Events in Plastic & Reconstructive Surgery Patients Randomized to Different Postoperative Anticoagulant Regimens.” The study Data Safety and Monitoring Board meets every 6 months to review unblinded data and provide recommendations (prior meetings May 5, 2017, December 7, 2017, May 7, 2018, and December 17, 2018).

Inclusion criteria will include adult (age ≥ 18) patients who have any plastic and reconstructive surgery under general anesthesia. Based on surgery and/or comorbidities, the necessary admission will be ≥ 2 days; this will also allow peak and trough aFXa levels to be drawn after the third dose. Exclusion criteria will include contraindication to use of enoxaparin, intracranial bleeding/stroke, hematoma or bleeding disorder, heparin-induced thrombocytopenia positive, creatinine clearance ≤ 30 mL/min, serum creatinine > 1.6 mg/dL, epidural anesthesia, or patients placed on nonenoxaparin chemical prophylaxis regimens at their surgeon’s discretion. The maximum enoxaparin dose that can be mixed into a 1.0 mL volume is 100 mg. We will exclude patients whose gross weight exceeds 150 kg. This criteria would allow a 150-kg patient to receive the initial 0.5-mg/kg study dose mixed in a volume of 1.0 mL, and would similarly allow multiple rounds of dose escalation to occur if the 150-kg patient had low aFXa levels.

Patients who meet inclusion criteria, provide informed consent, and are deemed eligible for randomization after their surgical procedure are randomized.

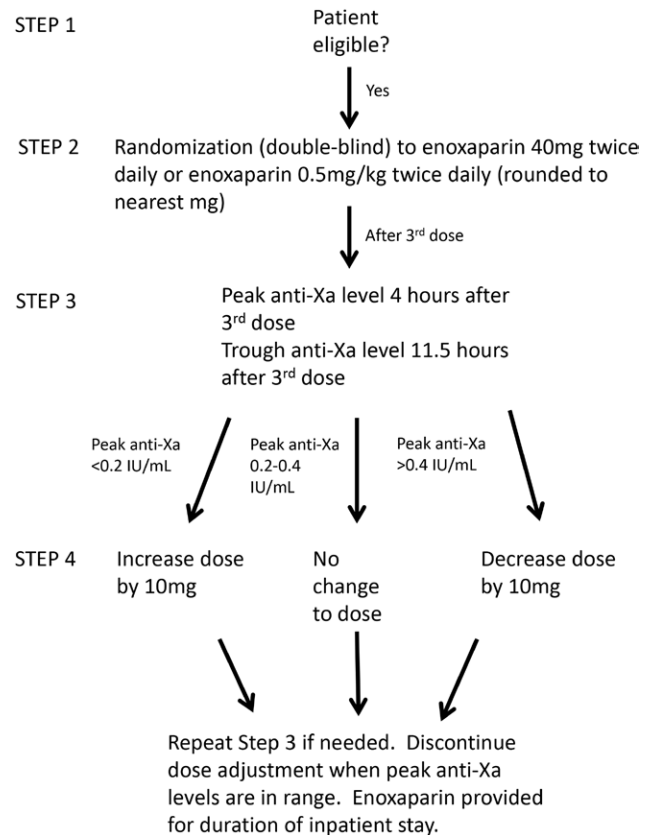


**Fig. 4.** Weight-based dose and aFXa levels among patients who received enoxaparin 40mg twice daily. Reprinted with permission from *Plast Reconstr Surg.* 2018;142:239–249.

The University of Utah Investigational Drug Services (IDS) Pharmacy randomizes patients to 1 of 2 blinded groups (enoxaparin 40mg twice daily or enoxaparin 0.5mg/kg twice daily, rounded to the nearest milligram). Randomization occurs using a random permuted block format. Block size is 4 or 6. The random permuted block format ensures treatment balance through the entire trial period. Enoxaparin is available as a 10mg/0.1mL solution. To maintain a consistent injection volume while allowing larger doses to be administered, all study drug is diluted to a 1.0mL volume. All doses are injected into the subcutaneous space.

Enoxaparin prophylaxis begins 8 hours after surgery. Prophylaxis is provided every 12 hours and is continued for the duration of inpatient stay. Timing of prophylaxis initiation and prophylaxis duration is compliant with existing data from the multicenter VTEPS study<sup>14,47–49</sup> and guidelines from the American Society of Plastic Surgeons.<sup>50</sup> All patients have sequential compression devices initiated before induction of surgical anesthesia and continued for the duration of inpatient stay. Peak and trough steady-state aFXa levels are drawn 4 and 11.5 hours after the third dose of enoxaparin (36 and 43.5 hours after surgery), respectively. These times were chosen because enoxaparin reaches steady state after 3 doses and reaches peak levels at 4 hours. The 11.5-hour trough was timed to avoid interference with the next planned dose at 12 hours after the prior dose. Goal peak aFXa levels are 0.2–0.4 IU/mL for twice daily dosing; this range has been shown to maximize VTE risk reduction while minimizing bleeding risk.<sup>30,31,36,39,43,51</sup> Patients have real-time aFXa-guided enoxaparin dose adjustment per Figure 5 performed by IDS Pharmacy; this will occur based on the peak steady-state aFXa level drawn 36 hours after surgery.

The study protocol in Figure 5 ends at patient discharge—patients do not undergo postdischarge dose optimization. Postdischarge chemical prophylaxis is not routinely provided, per existing VTE prevention guide-



**Fig. 5.** Clinical trial protocol for randomization, inpatient aFXa monitoring, and real-time enoxaparin dose adjustment.

lines from the American Society of Plastic Surgeons.<sup>50</sup> When provided, IDS Pharmacy coordinates provision of postdischarge enoxaparin to ensure patient, primary surgeon, and investigator blinding.

**Outcome Definitions**

The primary safety outcome for ADE minimization will be high (peak aFXa > 0.40 IU/mL) versus in range or low (peak aFXa ≤ 0.40 IU/mL) aFXa levels between groups. The primary effectiveness outcome will be in range or high (peak aFXa ≥ 0.20 IU/mL) versus low (peak aFXa < 0.20 IU/mL) aFXa levels between groups. The secondary safety outcome will be clinically relevant bleeding ADEs at 90 days after surgery, between groups. The secondary effectiveness outcome will be symptomatic VTE, confirmed with imaging, at 90 days after surgery, between groups.

Symptomatic VTE includes: (1) any deep venous thrombosis event, including upper limb, lower limb, or central veins (inferior vena cava, portal vein, etc.), which is confirmed with imaging including but not limited to duplex ultrasound, CT scan, or venogram and/or (2) any PE event that is confirmed with imaging, including but not limited to CT scan, venogram, or V/Q scan and/or (3) any autopsy-proven VTE and/or (4) 90-day mortality in which VTE cannot be excluded (eg, PEA arrest with no autopsy performed). Screening of asymptomatic patients will not be performed in line with current recommendations from the American College of Chest Physicians.<sup>7</sup>

**Table 1. SPIRIT Compliant Table Demonstrating the Schedule of Enrollment, Interventions, and Assessments**

Time Point	Study Period			
	Enrollment	Allocation		Postallocation
	Preoperative	Immediate	Postoperative	Inpatient
				Close-out
				90-d Follow-up
Enrollment:				
Eligibility screen	X			
Informed consent	X			
Surgeon willingness to randomize	X			
Allocation		X		
Interventions				
Enoxaparin 40 mg twice daily				↔
Enoxaparin 0.5 mg/kg twice daily				↔
Assessments				
2005 Caprini score and demographics	X			
Intraoperative details		X		X
Peak and trough aFXa				X
Postdose adjustment peak and trough aFXa (if needed)				X
Inpatient bleeding or VTE events				X
90-d chart review and phone call				X
90-d bleeding and 90-d VTE events				X

Clinically relevant bleeding ADEs will include any event that change the course of clinical care. Specifically, these events will be defined as: (1) unplanned return to the operating room for bleeding; (2) any need for blood or blood product transfusion; (3) bleeding requiring bedside drainage or interventional radiology drain placement; and (4) nonoperative bleeding that causes a cessation of enoxaparin prophylaxis before hospital discharge. We will collect data on 90-day VTE and 90-day bleeding ADEs. We will contact patients at 90 days via telephone or certified mail to identify events that were diagnosed or managed at other institutions. Time to event will be recorded for all secondary outcome events.

## ANALYSIS PLAN AND SAMPLE SIZE CALCULATION

We will identify patient-level factors that will include sex, age, body mass index, race, ethnicity, gross weight, creatinine, diabetes, smoking history, presence of cancer, history of trauma, 2005 Caprini score,<sup>52-54</sup> surgical duration, and duration of enoxaparin prophylaxis, in addition to relevant operative details. As we will have a large sample size and use randomization, the 2 study groups should be well balanced. Still, we will perform statistical comparisons to report descriptively, using the chi-squared or Fisher's exact test for dichotomous variables, student's *t* test for continuous variables, and Wilcoxon rank sum test for ordinal variables.

### Sample Size Calculations

The primary safety outcome will be absence of overanticoagulation [ $1 = \text{aFXa} \leq 0.40 \text{ IU/mL}$  (not overanticoagulated),  $0 = \text{aFXa} > 0.40 \text{ IU/mL}$  (overanticoagulated)]. This is the peak measurement at 36 hours postsurgery, taken in step 3 of Figure 5. The repeated measurements taken during dose adjustment (if needed) will not be used. A Poisson regression model for binary outcomes with robust standard errors will be fitted.<sup>55</sup> The primary predictor will be weight-based dose ( $1 = 0.5 \text{ mg/kg}$  twice daily,  $0 = 40 \text{ mg}$

twice daily), and the exponentiated regression coefficient for dose is a risk ratio. Randomization will ensure absence of confounding. In the unlikely event that the randomization did not generate balance on any of the patient-level baseline factors listed above, these factors will be added as covariates to increase precision of the comparison of the 2 dose groups.

The primary effectiveness outcome will be avoidance of underanticoagulation [ $1 = \text{aFXa} \geq 0.20 \text{ IU/mL}$  (not underanticoagulated),  $0 = \text{aFXa} < 0.20 \text{ IU/mL}$  (underanticoagulated)]. This is the peak measurement at 36 hours postsurgery, taken in step 3 of Figure 5. The repeated measurements taken during dose adjustment (if needed) will not be used. A Poisson regression model will be fitted. For the primary effectiveness outcome, a noninferiority hypothesis will be tested. The a priori noninferiority margin is set at an absolute 0.12 (12%) lower proportion of the "not underanticoagulated" outcome than the proportion for the standard dose (40 mg twice daily) group. Accepting an absolute 12% "worse than" is justified because adverse events do not accompany underanticoagulation in a 1:1 fashion. Noninferiority will be demonstrated if the 2-sided 95% CI around the difference in proportions (proportion not underanticoagulated in the weight-based dosing group minus the proportion not underanticoagulated in standard dose group) does not cross  $-0.12$ , or 12% "worse than."<sup>56</sup> The Poisson model expresses the result as a risk ratio or ratio of the 2 proportions. To obtain the risk difference, or difference in proportions, with a 95% CI, we will use marginal estimation after fitting the Poisson model. This method takes the 2 estimated proportions used in the risk ratio, subtracts them, and computes the CI used for noninferiority testing.

The safety and effectiveness outcomes are based on studies that demonstrate the optimal peak aFXa range to balance bleeding and VTE risk in patients who receive twice daily enoxaparin is 0.2–0.4 IU/mL.<sup>29-31,41-45</sup>

The 2 secondary outcomes will be bleeding ADEs and symptomatic VTE, both of which are binary variables. Poisson regression models will be computed. Because these

are rare events it is impossible to power the study to detect increases in risk between the dose groups. Thus, the model really only provides a way to demonstrate an unexpected, very large difference in risk. Even very large phase III pharmaceutical clinical trials are underpowered to detect differences in adverse events, because doing so requires unrealistic large sample sizes. Similarly, to what is done in large phase III trials, then we will report the adverse events descriptively, as proportions, with 2-sided 95% CIs.

The planned analysis will be performed as an intention-to-treat analysis.

### Sample Size Justification

Our pilot data include 115 patients who received enoxaparin 40 mg twice daily and had appropriately timed peak aFXa. On this regimen, 62.6% (n = 72) of patients had initial in range peak aFXa levels (0.2–0.4 IU/mL). 27.8% of patients (n = 32) had high levels (>0.4 IU/mL), and this included 11.3% (n = 13) of patients who had inadvertent therapeutic anticoagulation ( $\geq 0.5$  IU/mL). 9.6% (n = 11) of patients had low levels ( $\leq 0.2$  IU/mL). We assume that weight-based dosing at 0.5 mg/kg will increase the proportion of patients not overanticoagulated to 90%. We assume the proportion of absence of overanticoagulation will be 0.722 (1–0.278) in the standard dose group and 0.90 in the weight-based dose group. To detect this difference with 90% power using a 2-sided alpha 0.05 comparison, we require n = 100 per group.

For the noninferiority comparison, we assume both dose groups will have avoidance of underanticoagulation, or not underanticoagulated, proportions of 0.904 (1–0.096), so the difference is assumed to be 0. The noninferiority margin is 0.12 less than this, or –0.12 (this is the same as saying the weight-based group could have a not underanticoagulated proportion of 0.904–0.12 = 0.784). To achieve 90% power using a 2-sided alpha 0.05 comparison, using a 2-sided 95% CI around the difference in proportions, we require n = 127 per group, or total enrollment of N = 254.

For 90-day VTE and bleeding, the adverse events will be reported descriptively, so no power analysis is required. We considered the potential to power the study to examine clinically relevant bleeding events among patients who receive fixed versus weight-based enoxaparin dosing, but discarded this plan due to excessive sample size. Our preliminary data<sup>42</sup> show a 90-day rate of clinically relevant bleeding of 6.8% among patients who receive enoxaparin 40 mg twice daily. We assumed a clinically relevant bleeding rate of 3.2% in patients who receive weight-based twice daily dosing—3.2% was chosen as it is the rate of 90-day bleeding among patients who received fixed dose once daily prophylaxis,<sup>32</sup> and represents a reasonable goal bleeding rate for patients who receive twice daily prophylaxis. To achieve 80% power using a 2-sided alpha 0.05 comparison, we would need 575 patients per group (total N = 1,150). This enrollment exceeds what is reasonable for a single-site randomized control trial.

To have adequate power for all stated aims, then we will use n = 127 per group (total N = 254).

## CONCLUSION

This paper describes the methodologic and statistical justification for a randomized double-blind clinical trial adequately powered to identify the ideal twice daily enoxaparin dose regimen to optimize enoxaparin pharmacokinetics.

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