TITLE: A Randomized Controlled Trial Comparing Apixaban Versus Enoxaparin Following Microsurgical Breast Reconstruction

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Version # 3/ Version Date: 06-14-2022

SRC Initial Approval Date: 06-17-2020 (for Version dated 06-16-2020)

Summary of Changes

Page No./Section No.	Description of Change	Originator
Pg. 8/3.3.2	Specify history of alcohol and/or substance abuse prior to 6 months of enrollment	S. Meyer
Pg. 10/ 5.1	Specify VTE prophylaxis dose timing from 12 hours to 12-16 hours to be aligned with clinical practice.	S. Meyer
Pg. 12/ 8	Revised Study of Events to clarify when end of study timepoint, removed "w/diff" from CBC lab draw, added 90 day phone call	S. Meyer

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PROTOCOL SYNOPSIS

TITLE	A Randomized Controlled Trial Comparing Apixaban Versus Enoxaparin Following Microsurgical Breast Reconstruction
STUDY PHASE	Interventional
INDICATION	Unilateral or bilateral microsurgical breast reconstruction with free abdominal flaps (i.e. muscle-sparing transverse rectus abdominis musculocutaneous [TRAM] and/or deep inferior epigastric artery perforator [DIEP]) flap) and who are found to have a Caprini score of ≥7
INVESTIGATIONAL PRODUCT OR PROCEDURE	Apixaban, Enoxaparin
PRIMARY OBJECTIVE(S)	To examine the rate of bleeding events in patients receiving oral apixaban versus subcutaneous enoxaparin
SECONDARY OBJECTIVE(S)	To examine the rate of VTE events in patients receiving oral apixaban versus subcutaneous enoxaparin
TREATMENT SUMMARY	Eligible patients will be randomized to one of the following 2 treatment groups: 1) Apixaban 2.5 mg PO BID starting 12 hours after completing skin closure. 2) Enoxaparin 40 mg SC QD starting 12 hours after completing skin closure.
SAMPLE SIZE	100

SCHEMA

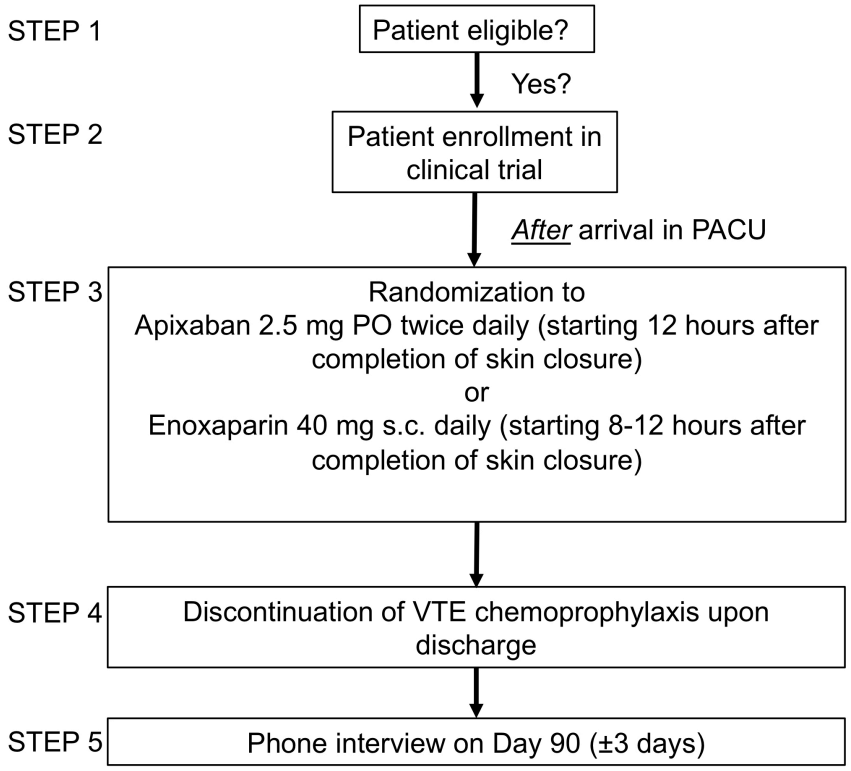

Figure 2. Clinical Protocol

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BID	Twice daily
CRF	Case report/Record form
CTCAE	Common Terminology Criteria for Adverse Events
DIEP	Deep inferior epigastric artery perforator
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
HIV	Human Immunodeficiency Virus
HTN	Hypertensions
IRB	Institutional Review Board
IV	Intravenous
PACU	Post-anesthesia care unit
PE	Pulmonary Embolism
PO	By mouth
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SC	Subcutaneous
TRAM	Transverse rectus abdominis musculocutaneous
ULN	Upper limit of normal
UNK	Unknown
VTE	Venous thromboembolism
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

To examine the rate of bleeding events in patients receiving oral apixaban versus subcutaneous enoxaparin.

1.2. Secondary Objectives

To examine the rate of VTE events in patients receiving oral apixaban versus subcutaneous enoxaparin.

2. BACKGROUND

2.1 Study Disease

Venous thromboembolism (VTE) is a common complication in patients undergoing surgery that can have devastating consequences (1-3). While symptomatic deep venous thrombosis (DVT) can lead to severe post-thrombotic syndrome in 10% of patients, symptomatic pulmonary embolism (PE) is the most common cause of preventable in-hospital death with a mortality rate of 10% within the hour and 17% at three months (4). The importance of prevention has been recognized and validated instruments, such as the Caprini Risk Assessment Model, have been introduced. These aid in clinical decision-making regarding chemoprophylaxis. The occurrence of 'breakthrough' VTE events, defined as the occurrence of VTE events despite guideline-compliant chemoprophylaxis, however, highlights the need for changes in clinical practice to improve clinical outcomes.

2.2 Study Agent/Device/Procedure

Review of enoxaparin mechanism and pharmacodynamics
Enoxaparin is a low molecular weight heparin commonly provided as chemical VTE prophylaxis in surgical patients. Enoxaparin accelerates the activity of antithrombin, which, in turn, accelerates the rate at which Factor Xa is inactivated. Factor Xa inactivation results in decreased conversion of prothrombin to thrombin. Inhibition of this critical step in the coagulation cascade decreases the likelihood that clot will form. Enoxaparin's peak response occurs at three to five hours after subcutaneous injection, with a half-life of seven hours. Enoxaparin metabolism occurs by metabolism in the liver and excretion via the kidneys. Patients with creatinine clearance of less than 30 mL/min demonstrate 30% decreased enoxaparin clearance. Enoxaparin exhibits linear pharmacokinetics and an inverse relationship between renal impairment and drug activity.

Review of apixaban mechanism and pharmacodynamics
Apixaban was introduced in 2014 and is a highly selective inhibitor of free and prothrombinase-bound FXa. It has a half-life of 8 to 15 hours and multiple pathways of elimination, including renal and fecal excretion with minimal drug-drug interactions. The recommended dose for VTE prophylaxis is 2.5mg PO BID. The superiority of apixaban over enoxaparin has been demonstrated in landmark trials of hip and knee replacement, where lower rates of VTE were seen without increased bleeding.

For clinicaltrials.gov compliance
Use of apixaban for VTE chemoprophylaxis following autologous breast reconstruction has not been approved by the FDA.

2.3 Rationale

Venous thromboembolism (VTE) continues to be a major patient safety issue after surgical intervention. Significant morbidity and mortality are associated with the development of VTE. With over 100,000 annual VTE-related deaths in the U.S., this disease entity represents the most common cause of preventable in-hospital death (10, 11). Furthermore, the associated economic burden is substantial, with annual costs to the U.S. healthcare system in excess of $7 billion (12).

The importance of VTE prevention has been recognized by organized plastic surgery. Significant resources have been

invested into raising awareness and improving VTE risk stratification and prophylaxis in patients undergoing plastic and reconstructive surgery. Initiatives such as the American Society of Plastic Surgeons (ASPS) VTE Task Force, the Plastic Surgery Foundation (PSF)-funded VTE Prevention Study (VTEPS) as well as initiatives by the American Association of Plastic Surgeons (AAPS) reflect the significant emphasis placed on this particular area of clinical research (3, 11, 13, 14). Important questions, however, remain unanswered and include issues such as appropriate dosing as well as duration of VTE chemoprophylaxis. Furthermore, mechanisms underlying 'breakthrough' VTE events, defined as VTE events despite guideline-compliant chemoprophylaxis, remain unknown. VTEPS demonstrated that despite daily enoxaparin prophylaxis 1 patient in 25 with a Caprini score >8 had a breakthrough VTE event (3). The occurrence of breakthrough VTE events highlights the need for an improved approach to VTE chemoprophylaxis.

VTE risk stratification and clinical research in other specialties have identified cancer patients as a particularly vulnerable patient population (15, 16). Of these, breast cancer patients represent the largest group treated by plastic surgeons. Symptomatic VTE has been reported in up to 4% of patients undergoing autologous reconstruction using abdominal flaps (17). An up to 20% rate of asymptomatic VTE after autologous reconstruction has been reported (18). In light of rising numbers of breast reconstruction in the U.S., with more than 18,000 autologous reconstructions in 2013, a 35% increase in the number of annual breast reconstructions since 2000, and over 106,000 breast reconstructions in 2015 alone, the number of patients at risk for VTE is alarmingly high (19-21). It is important to note that an increased rate of DVT formation has been reported following autologous vs. implant-based breast reconstruction despite guideline-compliant prophylaxis (22). These findings are particularly relevant in light of an increasing number of patients undergoing prophylactic bilateral mastectomy with immediate reconstruction. As such, it is of no surprise that the ASPS VTE Task Force identified "major breast reconstruction" as a procedure warranting additional prophylactic considerations (11). Given the large number of patients at risk, particular emphasis on understanding the processes leading to VTE development in this patient population is warranted. A recent retrospective study in over 1500 patients who underwent body contouring procedures (LMWH [N=454]; rivaroxaban [N=703], apixaban [N=415]) demonstrated similar rates of bleeding-related adverse events (37).

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

- **Prevention**: protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition
- **Parallel**: one of two groups in parallel for duration of study.
    - 2 intervention arms.
    - **Open**: no masking is used
    - Study is randomized.
    - Safety/Efficacy; Pharmacokinetics.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Adult (>18 years) women who are scheduled to undergo unilateral or bilateral microsurgical breast reconstruction with free abdominal flaps (i.e. muscle-sparing transverse rectus abdominis

musculocutaneous [TRAM] and/or deep inferior epigastric artery perforator [DIEP]) flap) and who are found to have a Caprini score of ≥6

3.1.2 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 NSAIDs or other anticoagulant intake within 7 days of surgery

3.2.2 Use of other Investigational Agents is prohibited.

3.2.3 Active bleeding, history of bleeding disorder, coagulopathy, heparin-induced thrombocytopenia, liver disease, renal disease (creatinine clearance ≤ 30 mL/min; serum creatinine >1.6 mg/dL), major neurosurgical intervention (brain/spine) within the past 90 days, ophthalmologic procedure within the past 90 days, uncontrolled hypertension, history of alcohol and/or substance abuse prior to 6 months of enrollment, or need for therapeutic anticoagulation

3.2.4 Contraindication to the use of apixaban or enoxaparin

3.2.5 Pregnant or nursing patients will be excluded from the study.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Randomization Procedures

Attending surgeon and assistant surgeons will be blinded to the randomization status during surgical procedure. Randomization will be determined using a pre-specified randomization list. Once surgery is complete, the study coordinator will notify the surgeon of the randomization ARM the patient is assigned to upon their arrival in post-anesthesia care unit (PACU).

3.5 Study Timeline

Primary Completion:
The study will reach primary completion 18 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion 24 months from the time the study opens to accrual.

4. TREATMENT PLAN

Adult (>18 years) women who are scheduled to undergo unilateral or bilateral microsurgical breast reconstruction with free abdominal flaps (i.e. muscle-sparing transverse rectus abdominis musculocutaneous [TRAM] and/or deep inferior epigastric artery perforator [DIEP]) flap) and who are found to have a Caprini score of ≥6 will be approached by the clinical research coordinator during the preoperative clinic visit. Informed consent for randomization and study participation will be obtained.

Exclusion criteria will include contraindication to the use of apixaban or enoxaparin, active bleeding, history of bleeding disorder, coagulopathy, heparin-induced thrombocytopenia, liver disease, renal disease (creatinine clearance

≤ 30 mL/min; serum creatinine >1.6 mg/dL), major neurosurgical intervention (brain/spine) within the past 90 days, ophthalmologic procedure within the past 90 days, uncontrolled hypertension, history of alcohol and/or substance abuse, or need for therapeutic anticoagulation.

Eligible patients will be randomized to one of the following 2 treatment groups (Figure 2):

1) Apixaban 2.5 mg PO BID starting 12 hours after completing skin closure.
2) Enoxaparin 40 mg SC QD starting 12 hours after completing skin closure.

Patients will be assigned to the respective study groups postoperatively upon arrival in the PACU. Hence, surgeons are blinded at the time of surgery as to study group assignment. Chemoprophylaxis will continue for the duration of the hospitalization. Planned timing of prophylaxis initiation with apixaban and enoxaparin is in alignment with published data from the multicenter VTEPS study, respectively (3, 8, 9, 38). Prophylaxis duration is compliant with guidelines from the American Society of Plastic Surgeons (11). All patients will receive mechanical prophylaxis in the form of sequential compression devices prior to the induction of general anesthesia and continued for the duration of inpatient stay.

The treatment period spans the duration of inpatient hospitalization. While hospitalized, patients will be evaluated daily for symptomatic VTE (DVT and/or PE) and bleeding events. After hospital discharge, patients will be encouraged to report all adverse events (AEs) including, but not limited to, signs/symptoms of DVT/PE and bleeding. Suspected DVT/PE will be evaluated with the appropriate diagnostic assessment, including but not limited to Duplex sonography, chest CT-angiography, or V/Q scan. A mandatory phone interview will take place on Day 90 (±3 days) to confirm that no 90-day events had been diagnosed or were managed by another institution.

4.1 General Concomitant Medication and Supportive Care Guidelines

No additional medication beyond VTE chemoprophylaxis (i.e. enoxaparin vs. apixaban) will be administered as part of the trial. VTE chemoprophylaxis is a normal part of clinical management following autologous breast reconstruction. The safety profile of apixaban will be studies in patients at highest risk for development of VTE, i.e. Caprini score ≥6.

4.2 Criteria for Removal from Study

The experiment will terminate if the subject wishes to terminate study treatment or has adverse reaction to the medication that the treating physician deems withdrawal is necessary, or patient withdrawal of consent.

4.3 Alternatives

The alternative is to not participate and receive the standard treatment of subcutaneous anticoagulant postoperatively.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

We previously demonstrated that the majority of plastic surgery patients receive inadequate enoxaparin prophylaxis using fixed daily dosing (5). A follow-up study demonstrated a statistically significant reduction in postoperative VTE rate following twice daily administration of enoxaparin (6). The observed clinical differences are explained by differences in the rate of in-range peak anti-factor Xa levels (7).

Although enoxaparin is effective, disadvantages include the need for subcutaneous injection as well as dose adjustment based on anti-factor Xa levels. A potentially better alternative is the use of oral, direct factor Xa inhibitors. Importantly, this group has demonstrated superior outcomes in the orthopedic population when compared to enoxaparin (8, 9). Hence, it appears prudent to examine their role in the plastic surgery population.

This project will identify plastic surgery patients who meet criteria for postoperative VTE chemoprophylaxis and 1)

identify the rate of adverse drug events (ADE) following oral apixaban administration, 2) examine the rate of bleeding events in patients receiving oral apixaban versus subcutaneous enoxaparin, and 3) examine the rate of VTE in each group.

Review of enoxaparin mechanism and pharmacodynamics
Enoxaparin is a low molecular weight heparin commonly provided as chemical VTE prophylaxis in surgical patients. Enoxaparin accelerates the activity of antithrombin, which, in turn, accelerates the rate at which Factor Xa is inactivated. Factor Xa inactivation results in decreased conversion of prothrombin to thrombin. Inhibition of this critical step in the coagulation cascade decreases the likelihood that clot will form. Enoxaparin's peak response occurs at three to five hours after subcutaneous injection, with a half-life of seven hours. Enoxaparin metabolism occurs by metabolism in the liver and excretion via the kidneys. Patients with creatinine clearance of less than 30 mL/min demonstrate 30% decreased enoxaparin clearance. Enoxaparin exhibits linear pharmacokinetics and an inverse relationship between renal impairment and drug activity.

Review of apixaban mechanism and pharmacodynamics
Apixaban was introduced in 2014 and is a highly selective inhibitor of free and prothrombinase-bound FXa. It has a half-life of 8 to 15 hours and multiple pathways of elimination, including renal and fecal excretion with minimal drug-drug interactions. The recommended dose for VTE prophylaxis is 2.5mg PO BID. The superiority of apixaban over enoxaparin has been demonstrated in landmark trials of hip and knee replacement, where lower rates of VTE were seen without increased bleeding.

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance
Intervention Description
Patients will be assigned to the respective study groups postoperatively upon arrival in the PACU. Hence, surgeons are blinded at the time of surgery as to study group assignment. Chemoprophylaxis will continue for the duration of the hospitalization. Planned timing of prophylaxis initiation with apixaban and enoxaparin is in alignment with published data from the multicenter VTEPS study, respectively (3, 8, 9, 38). Prophylaxis duration is compliant with guidelines from the American Society of Plastic Surgeons (11). All patients will receive mechanical prophylaxis in the form of sequential compression devices prior to the induction of general anesthesia and continued for the duration of inpatient stay.

The treatment period spans the duration of inpatient hospitalization. While hospitalized, patients will be evaluated daily for symptomatic VTE (DVT and/or PE) and bleeding events. After hospital discharge, patients will be encouraged to report all adverse events (AEs) including, but not limited to, signs/symptoms of DVT/PE and bleeding. Suspected DVT/PE will be evaluated with the appropriate diagnostic assessment, including but not limited to Duplex sonography, chest CT-angiography, or V/Q scan. A mandatory phone interview will take place on Day 90 (±3 days) to confirm that no 90-day events had been diagnosed or were managed by another institution.

Arms/Groups:
Group A: Apixaban 2.5 mg PO BID starting 12-16 hours after completing skin closure.
Group B: Enoxaparin 40 mg SC QD starting 12-16 hours after completing skin closure.

5.2 Availability

Stanford Hospital & Clinics has both agents readily available.

5.3 Agent Ordering

The agent will be requested through the EPIC physician ordering system.

5.4 Agent Accountability

The agent will be kept secure as standard process for the pharmacy so as to avoid access to unauthorized persons.

6. DOSE MODIFICATIONS

We do not plan to adjust medication dose. In the absence of postoperative bleeding, the medication will be administered per protocol. The medication will be withheld and/or discontinued, however, in the setting of major bleeding or clinically relevant nonmajor bleeding (for definitions see 7.1.).

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

The primary safety outcome is bleeding during the treatment period or until 2 days after the last dose of the study medication was administered (Lassen et al. NEJM 2020;26:2487-2498). Bleeding is categorized as major, clinically relevant nonmajor, or minor bleeding and as the composite of major and clinically relevant nonmajor bleeding. The definition of major bleeding is acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding. Clinically relevant nonmajor bleeding includes acute, clinically overt episodes such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis that does not meet the criteria for major bleeding. Bleeding is categorized as minor if it is clinically overt but is not adjudicated as major or clinically relevant nonmajor bleeding.

7.2 Adverse Event Reporting

All bleeding/thrombotic Adverse Events will be tracked by the research team using an adverse event log. All unanticipated adverse events and SAE's will be reported to the IRB. Annual summaries of adverse events will be reported to the IRB.

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 after the last dose of the study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. STUDY CALENDAR

	Pre-Study	12 -16 hours post surgery ending at time of inpatient discharge	Time of hospital discharge	90 days post surgery
Investigational Agent [1,2]		X		
Informed consent	X			
Demographics	X			
Medical history	X			
Concurrent meds	X			
Physical exam	X	X		
Vital signs	X	X		
Height	X			
Weight	X			
Caprini Score	X			
CBC	X	X		
Serum chemistry	X	X		
Adverse event evaluation			X	X
90 Day Phone Call				X

1. Apixaban 2.5 mg PO BID starting 12-16 hours after completing skin closure.
2. Enoxaparin 40 mg SC QD starting 12-16 hours after completing skin closure

9. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

Primary Outcome Measure: The primary study outcome is defined as overall bleeding event risk 90 days post-randomization. Secondary patient-oriented outcomes include risk of VTE events

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- **Time Frame**: 90 days post-randomization.
- **Safety Issue**: We are not measuring a safety issue.

9.1 Primary and Secondary Outcome measures

The primary study outcome is defined as overall bleeding event risk 90 days post-randomization. Secondary patient-oriented outcomes include risk of VTE events. Tertiary outcomes include: length of stay, location of patient on day 90 of follow up (home vs. SNF, etc), and clinically significant wound complications (infection, dehiscence, flap loss).

Process measures to be collected include time to starting anticoagulation after completion of skin closure, number of days patients received anticoagulation treatment, and timing of phone interview follow up.

Conservative estimates from recent retrospective study in over 1500 patients who underwent body contouring procedures (LMWH [N=454]; rivaroxaban [N=703], apixaban [N=415]) are used for our power analysis (37). Using standard formulas, with 80% power to detect a non-inferiority margin of -0.075, and assuming a 1.32% baseline in bleeding events among patients dosed on daily enoxaparin compared with a 1.73% rate of bleeding in direct oral anticoagulant (DOAC) arm patients over 90 days, our analysis expects enrollment size of 37 patients per arm. We conservatively estimate a 25% dropout rate over the course of the study, which results in a sample size of 100 (50 patients per arm).

The primary conclusions of this project will be analyzed based on intention-to-treat where all randomized patients will be analyzed within the groups they were originally allocated to. Two-sided 5% significance levels will be used to identify statistically significant results. Unadjusted analysis of the bleeding risk in apixaban use will be assessed using an exact Pearson chi-squared test. The outcome will be reported as an odds ratio with 95% confidence intervals. Baseline prognostic variables including age, BMI, Caprini score, Elixhauser comorbidity index score, procedure duration, unilateral vs. bilateral will be ascertained upon enrollment and reported by our study group. A subsequent covariate adjusted analysis will be undertake with an adjusted logistic regression model.

10. REGULATORY CONSIDERATIONS

10.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

10.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious

adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

10.3 Data Management Plan

The Protocol Director, or his designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the REDCap database system and will be maintained by the protocol director. CRFs will be kept in a locked office, only accessible to the research team.Study specific Case

11. STATISTICAL CONSIDERATIONS

11.1 Statistical Design

The primary study outcome is defined as overall bleeding event risk 90 days post-randomization. Secondary patient-oriented outcomes include risk of VTE events. Tertiary outcomes include: length of stay, location of patient on day 90 of follow up (home vs. SNF, etc), and clinically significant wound complications (infection, dehiscence, flap loss).

Process measures to be collected include time to starting anticoagulation after completion of skin closure, number of days patients received anticoagulation treatment, and timing of phone interview follow up.

Conservative estimates from recent retrospective study in over 1500 patients who underwent body contouring procedures (LMWH [N=454]; rivaroxaban [N=703], apixaban [N=415]) are used for our power analysis (37). Using standard formulas, with 80% power to detect a non-inferiority margin of -0.075, and assuming a 1.32% baseline in bleeding events among patients dosed on daily enoxaparin compared with a 1.73% rate of bleeding in direct oral anticoagulant (DOAC) arm patients over 90 days, our analysis expects enrollment size of 37 patients per arm. We conservatively estimate a 25% dropout rate over the course of the study, which results in a sample size of 100 (50 patients per arm).

The primary conclusions of this project will be analyzed based on intention-to-treat where all randomized patients will be analyzed within the groups they were originally allocated to. Two-sided 5% significance levels will be used to identify statistically significant results. Unadjusted analysis of the bleeding risk in apixaban use will be assessed using an exact Pearson chi-squared test. The outcome will be reported as an odds ratio with 95% confidence intervals. Baseline prognostic variables including age, BMI, Caprini score, Elixhauser comorbidity index score, procedure duration, unilateral vs. bilateral will be ascertained upon enrollment and reported by our study group. A subsequent covariate adjusted analysis will be undertake with an adjusted logistic regression model.

11.2 Interim Analyses

Interim analysis will occur after the first ten subjects are enrolled. At this timepoint it is expected that we should have preliminary data to analyze.

11.3 Randomization

Attending surgeon and assistant surgeons will be blinded to the randomization status during surgical procedure. Randomization will take place using a pre-specified randomization list. The study coordinator will notify the surgeon which ARM the patient is randomized to upon their arrival in post-anesthesia care unit (PACU).

11.4 Descriptive Statistics and Exploratory Data Analysis

The primary study outcome is defined as overall bleeding event risk 90 days post-randomization. Secondary patient-oriented outcomes include risk of VTE events. Tertiary outcomes include: length of stay, location of patient on day 90 of follow up (home vs. SNF, etc), and clinically significant wound complications (infection, dehiscence, flap loss).

Process measures to be collected include time to starting anticoagulation after completion of skin closure, number of days patients received anticoagulation treatment, and timing of phone interview follow up.

Conservative estimates from recent retrospective study in over 1500 patients who underwent body contouring procedures (LMWH [N=454]; rivaroxaban [N=703], apixaban [N=415]) are used for our power analysis (37). Using standard formulas, with 80% power to detect a non-inferiority margin of -0.075, and assuming a 1.32% baseline in bleeding events among patients dosed on daily enoxaparin compared with a 1.73% rate of bleeding in direct oral anticoagulant (DOAC) arm patients over 90 days, our analysis expects enrollment size of 37 patients per arm. We conservatively estimate a 25% dropout rate over the course of the study, which results in a sample size of 100 (50 patients per arm).

The primary conclusions of this project will be analyzed based on intention-to-treat where all randomized patients will be analyzed within the groups they were originally allocated to. Two-sided 5% significance levels will be used to identify statistically significant results. Unadjusted analysis of the bleeding risk in apixaban use will be assessed using an exact Pearson chi-squared test. The outcome will be reported as an odds ratio with 95% confidence intervals. Baseline prognostic variables including age, BMI, Caprini score, Elixhauser comorbidity index score, procedure duration, unilateral vs. bilateral will be ascertained upon enrollment and reported by our study group. A subsequent covariate adjusted analysis will be undertake with an adjusted logistic regression model.

12. REFERENCES

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APPENDICES

APPENDIX A**: Participant Eligibility Checklist**

Protocol Title:	A Randomized Controlled Trial Comparing Apixaban Versus Enoxaparin Following Microsurgical Breast Reconstruction
Protocol Number:	49355
Principal Investigator:	Arash Momeni

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Adult (>18 years) women who are scheduled to undergo unilateral or bilateral microsurgical breast reconstruction with free abdominal flaps (i.e. muscle-sparing transverse rectus abdominis musculocutaneous [TRAM] and/or deep inferior epigastric artery perforator [DIEP]) flap) and who are found to have a Caprini score of ≥6	☐	☐	
2. Ability to understand and the willingness to sign a written informed consent document.	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. NSAIDs or other anticoagulant intake within 7 days of surgery	☐	☐	
2. Use of other Investigational Agents is prohibited	☐	☐	
3. Active bleeding, history of bleeding disorder, coagulopathy, heparin-induced thrombocytopenia, liver disease, renal disease (creatinine clearance ≤ 30 mL/min; serum creatinine >1.6 mg/dL), major neurosurgical intervention (brain/spine) within the past 90 days, ophthalmologic procedure within the past 90 days,	☐	☐	

uncontrolled hypertension, history of alcohol and/or substance abuse, or need for therapeutic anticoagulation			
4. Contraindication to the use of apixaban or enoxaparin	☐	☐	
5. Pregnant or Nursing	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	