**The Impact of Topical Tranexamic Acid in Breast Reconstruction**
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**Principal Investigator (Sponsor-Investigator)**
Merisa Piper, MD
University of California, San Francisco
[redacted]

**Statistician**
Chiung-Yu Huang, PhD
UCSF Surgery Biostatistics Core


**Revision History**

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|---|---|
| Version 2 | 08/12/2022 |
| Version 3 | 09/27/2022 |

**Protocol Signature Page**

1. I agree to follow this protocol version as approved by the UCSF Protocol Review and Monitoring Committee (PRMC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

**UCSF Principal Investigator**

Merisa Piper

Printed Name

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Signature

1/26/2024

Date

**Abstract**

| | |
|---|---|
| Title | The impact of topical Tranexamic Acid in reconstructive post-oncologic breast surgery |
| Study Description | Improvement in bleeding and bruising has been described by using both intravenous and topical off-label applications of Tranexamic Acid (TXA) in many surgical fields. The proposed prospective study will evaluate the utility of topical tranexamic acid in decreasing hematoma and seroma rates, drain output, and ecchymosis in post-mastectomy breast reconstruction patients. This novel use of TXA in breast surgery may provide a simple, cost-effective, and safe way to improve outcomes and satisfaction for our breast cancer patients. |
| Phase of Study | Phase 2 |
| Investigational Products | Tranexamic Acid (Topical application) |
| Study population | Female patients > 18 years old undergoing bilateral mastectomy with reconstruction or complex closure |
| Primary Objective | To investigate whether topical tranexamic acid may impact rates of seroma, hematoma, severe bruising, and drain output in the post-mastectomy reconstructive population |
| Sample Size | The goal enrollment is 150 patients undergoing bilateral mastectomy, or 300 breasts. Given that the literature cites a hematoma rate of up to 5% in post mastectomy patients, if we aim for complete reduction with TXA, we will need at least 150 per group to be adequately powered to detect that difference (alpha 0.05, beta 0.2). However, since complete reduction is not realistic, we will aim to recruit as many as possible with a minimum goal of 150 patients, which will give us 300 breasts total such that 150 breasts will receive TXA and 150 breasts saline. |
| Duration of Study Treatment | Participants will only be treated intraoperatively at the time of surgery with topical TXA to one breast pocket. |

| | |
|---|---|
| Duration of Follow up | We routinely follow post-mastectomy patients up to 1 year after their surgery. The standard post-operative follow-up regimen includes appointments at 1 week, 2 weeks, 6 weeks, 3 months, and 1 year, followed by yearly appointments thereafter. However, the schedule and number of visits will vary by patient. Patients in this study will be assessed at their regularly scheduled visits up to one year post-operatively. |
| Unique Aspects of this Study | This study is the first in the United States to evaluate the impact of topical Tranexamic Acid on hematoma, seroma, drain output, drain duration, and subjective bruising following post-mastectomy breast reconstruction, utilizing each patient as their own internal control. |

## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| SAE | Serious Adverse Event |
| DSMC | Data and Safety Monitoring Committee |
| HDFCCC | Helen Diller Family Comprehensive Cancer Center |
| HIPAA | Health Insurance Portability and Accountability Act |
| IRB | Institutional Review Board |
| IV | intravenous |
| TXA | Tranexamic Acid |

## Table of Contents

# 1 Introduction

## 1.1 Background on Indication

Post-mastectomy breast reconstruction has significant physical, mental and emotional benefits for breast cancer patients[1]. However hematoma, seroma and bruising are common complications given the highly vascularized nature of breast tissue[2]. These events can compromise the reconstruction, as well as potentially delay cancer treatments including chemotherapy and radiation by predisposing the patient to infection and wound complications. The hematoma and subsequent reoperation rate in breast surgery has been cited from 2-5% [2], thus topical hemostatic agents are often used intraoperatively. However, these agents are usually expensive, come in varying forms, and difficult to regulate. Prior studies in orthopedics, plastic surgery, and trauma have shown a significant reduction in bleeding, ecchymosis, and need for transfusions with use of Tranexamic Acid (TXA)[3-12]. TXA is a synthetic amino acid that blocks plasminogen conversion to plasmin, to prevent fibrinolysis and stabilize clot formation. Improvement in bleeding and bruising has been described utilizing both intravenous and topical off-label applications of TXA[6, 12]. In breast surgery there have been mixed results to preliminary retrospective studies of both intravenous and topical tranexamic acid, with some decreases in hematoma and seroma rates, and drain volumes[13-15]. The proposed prospective trial will evaluate the efficacy of topical TXA in decreasing hematoma and seroma rates, drain output, drain duration, and ecchymosis in bilateral post-mastectomy breast reconstruction patients. Every patient will serve as their own control. This novel use of TXA in breast surgery may provide a simple, cost-effective, and safe way to improve outcomes in breast reconstruction patients.

## 1.2 Background on the Investigational Product(s) and Associated Known Toxicities

TXA is a synthetic amino acid that blocks plasminogen conversion to plasmin to stabilize clot formation [16]. Despite the fact that TXA is only FDA-approved for hemophilia patients to reduce hemorrhage and need for replacement therapy following tooth extraction [16], many high powered double-blind randomized trials have published their results using TXA in other surgical specialties. Prior orthopedic arthroplasty studies have shown that a single intraoperative dose of TXA prior to incision significantly decreases blood loss and transfusion requirements without associated thrombotic complications [6, 7, 11, 17]. These have shown that not only intravenous, but also directly infiltrating the joint topically can decrease bleeding [6, 12]. Furthermore, there have not been any report of increased systemic thrombosis when used topically. In plastic surgery, TXA is routinely dosed intravenously prior to incision for pediatric craniosynostosis cases to minimize blood loss, decrease transfusion requirements, and shorten length of hospital stay [3, 4, 9]. The literature also shows when used topically it can significantly decrease bruising and bleeding in rhinoplasty, rhytidectomy, and liposuction [8, 10, 18, 19].

More recently, there have been retrospective studies in breast plastic and oncologic surgery evaluating the use of TXA without any evidence of thrombotic complications. Weissler et al published a retrospective review of immediate post-mastectomy tissue

expander placement which showed a statistically significant decrease in hematoma with intravenous TXA administration[13]. Perhaps most pertinent for our study is the small trial from Ausen et al in the Netherlands in which they examined topical moistening of mastectomy flaps with a dilute TXA solution. They found no complications were related to topical administration of TXA relative to the control group[15]. This small study trended toward decreasing hematoma rates and drain volumes, and inspired our own study design of using each patient as their own internal control. We hope to build off this study given our large volume of mastectomies, and low risk profile of utilizing topical TXA. Additionally, designing the study such that each patient receives a control and experimental dose (saline on one side, TXA on the other) will help us to control for any confounding patient factors and further validate our results.

Given the mechanism of action of TXA, there is the theoretical complication of perpetuating thrombotic events due to inhibition of clot breakdown[16]. There have been no documented events of venous thromboembolism in relation to topical administration of TXA in plastic surgery procedures, which are the most relevant to our proposed study[6, 8, 14, 15, 18]. One prior study in trauma patients showed an increased risk of pulmonary embolism/or deep venous thrombosis with TXA[20]. However, this was a study regarding repetitive intravenous dosing, and in a uniquely sick patient population in extremis, with disseminated intravascular coagulation due to acute traumatic blood loss and therefore not directly applicable to our proposed study. Other side effects associated with intravenous tranexamic acid include hypersensitivity reactions, seizures, visual disturbances, and dizziness[16]. The latter three would not apply to our study given that with topical tranexamic acid, the drug will not cross the blood brain barrier and thus would not elicit neurologic adverse effects.

### 1.3 Rationale for the Proposed Study

The proposed prospective trial will evaluate the utility of topical tranexamic acid in decreasing hematoma, seroma, and ecchymosis in post-mastectomy breast reconstruction patients. We currently use several topical intraoperative hemostatic agents including Arista, Surgicell, and Teseal. These have varying efficacy, inconsistent data, and greater cost than TXA which is produced in many generic formulations. Given that prior literature demonstrates TXA is effective in improving hematoma and bleeding outcomes with no proven risk, especially when applied topically, our goal is to investigate the potential of topical TXA to decrease rates of post-operative bleeding, hematoma, seroma, drain volume, and bruising. This work is significant because TXA offers a cheaper, time-efficient, and simple way to potentially improve outcomes post-mastectomy. Each patient will serve as their own internal control by design, there is no greater risk to any one patient in the study over others. Additionally, if we find that TXA helps with post-operative outcomes and offers a cheaper alternative to various other hemostatic agents on the market, this benefits the hospital and patient.

### 1.4 Rationale for the TXA Dose Selection/Regimen

Each patient will have one breast exposed to TXA and the other to saline. Prior literature has safely demonstrated the topical application of 1 gram of TXA in patients

undergoing joint replacement surgery[12]. TXA is readily available in the anesthesia cart of the operating room in a sterile, single-dose 1g/ml vial that needs to be reconstituted in 1ml of saline. This can then be added to 40ml of 0.9% normal saline to dilute it to 25mg/ml TXA solution. 20cc of this can then be infiltrated into the breast pocket, which would only expose the patient to 500mg of TXA to that side. With prior evidence to suggest 1 gram of TXA is safe, we are well within the range of TXA that can be safely administered. Additionally, this 20cc of solution can easily fit into a breast pocket without leaking and/or affecting skin closure. 20cc of 25mg/ml solution was also previously described in the small trial by Ausen et al and serves as the model for this study design[15].
There will only be one application of topical TXA and this will be administered intraoperatively, without subjecting patients in theory to systemic risks.

## 2 Study Objectives

### 2.1 Hypothesis

Given the use of topical tranexamic acid in reducing bleeding and bruising in other surgical specialties, we believe that topical tranexamic acid can improve post-operative outcomes after breast cancer surgery in a cost-effective manner. We hypothesize that the use of topical TXA in the breast pocket prior to closure will lead to a significantly lower rate of breast hematoma or seroma requiring intervention, decrease overall drain output, and decrease subjective bruising when compared to the control breasts.

### 2.2 Primary Objective and Endpoint(s)

The primary objective of this study is to evaluate the impact of topical TXA versus control (saline) on key post-operative outcome measures. These include hematoma, seroma, drain output, drain duration, bruising, and reoperation.

| Primary Objective | Endpoint(s) | Time Frame |
|---|---|---|
| 1. To evaluate the impact of TXA on hematoma rates compared to control | Presence of hematoma in 30 day period | From application in the operating room to 30 days of follow up |
| 2. To evaluate the impact of TXA on seroma rates compared to control | Presence of seroma in 3 month period | From application in the operating room to 3 months of follow up |

## 2.3 Secondary Objective(s) and Endpoint(s)

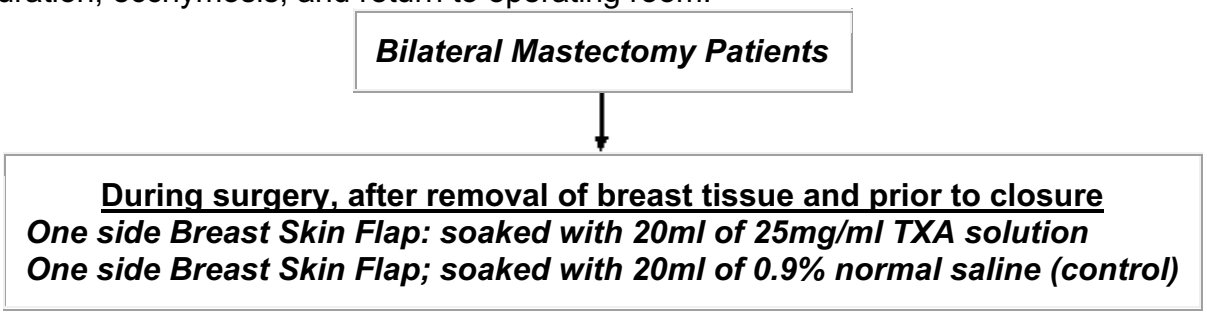
| Secondary Objective | Endpoint(s) | Time Frame |
|---|---|---|
| 1. To evaluate the impact of TXA on patient and provider rating of bruising, comparing the TXA side to the control side | • Ecchymosis will be compared between the right and left side at each post operative visit and documented. The observer will be blinded to the laterality of TXA | From application in the operating room to 30 days of follow up |
| 2. To evaluate the impact of TXA on total drain output in the first post operative day | • Total drain output over the life of the drain, compared between control and study groups | From drain placement in the operating room to discharge on POD1 |
| 3. To evaluate the impact of TXA on total drain duration | • Total drain duration compared between control and study groups | From drain placement in the operating room to removal of the drain |

# 3 Study Design

## 3.1 Characteristics

We propose a prospective, placebo-control trial looking at the effect of topical tranexamic acid on post-operative bleeding, hematoma, seroma, drain output, and bruising in post-mastectomy breast reconstruction. We will recruit patients undergoing bilateral mastectomy at our institution. Patients will be excluded if they have previous history of bleeding or coagulation disorders. Each patient will serve as their own internal control, with one side receiving saline and the other TXA. During surgery and prior to wound closure, we will moisten the wound surface of one side with 20 cc of dilute TXA 25mg/ml solution, and the contralateral with 20cc of saline. Demographics, cancer details, and surgical characteristics will be collected. Outcomes will we assess include hematoma, seroma, reoperation, drain duration, and degree of ecchymosis will be recorded post-operatively for analysis over a 3-month period. The primary outcome will

be presence of hematoma. Secondary outcomes will include seroma, drain output and duration, ecchymosis, and return to operating room.




The surgeon will mix the TXA solution and pass onto the surgical field (detailed in a later section). After completion of the bilateral mastectomy, the plastic surgeon will perform their portion of the procedure. Immediately prior to final closure, 20ml of 25mg/ml TXA solution will be infiltrated into one breast pocket. 20ml of 0.9% normal saline will be infiltrated into the other breast pocket. No other hemostatic agents will be used. The sidedness of the TXA administration will be documented by the surgery team in our record but kept confidential from the surgery clinic staff to prevent bias at post-operative assessments. The solutions will be allowed to dwell while performing incisional closure, and the solutions will be evacuated by the Jackson-Pratt drain when placed to bulb suction at the end of the case. Post-procedure, each patient will be provided with standard post-operative instructions. They will be followed post-operatively for up to 1 year.

### 3.2 Sample Size

The goal enrollment is 150 patients, 300 breasts. Given that the literature cites a hematoma rate of up to 5% in mastectomy patients, if we aim for complete reduction with TXA, we will need at least 150 per group to be adequately powered to detect that difference (alpha 0.05, beta 0.2). However, since complete reduction is not realistic, we will aim to recruit as many as possible but with a minimum goal of 150 patients (150 breasts will receive TXA, 150 breasts will receive saline).

### 3.3 Eligibility Criteria

Patients must have baseline conditions reviewed prior to enrolling and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the required post-operative follow up. Written informed consent must be obtained from the patient prior to enrollment. Per standard of care, patients will not receive chemotherapy or radiation treatment within 4 weeks of the operation. The following criteria apply to all patients enrolled into the study unless otherwise specified.

#### 3.3.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Histologically confirmed breast malignancy OR increased risk for breast cancer

2. Age ≥ 18 years
3. Scheduled to undergo bilateral mastectomy with plastic surgery closure or reconstruction
4. Ability to understand a written informed consent document, and the willingness to sign it
5. At least 4 weeks post-completion of chemotherapy or radiation therapy

### 3.3.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Any significant medical condition or laboratory abnormalities, which places the subject at unacceptable risk if she were to participate in the study
2. Any history of thromboembolic disease
3. Current anticoagulant use
4. Current use of chlorpromazine due to label contraindication
5. Current use of any prothrombotic medical products due to label contraindication
6. Documented or reported allergic reaction to tranexamic acid
7. Male patients

## 3.4 Inclusion of Women and Minorities

### 3.4.1 Eligibility of Women and Minorities

Women of any race, or ethnicity are eligible for this study

### 3.4.2 Recruitment of Minority Groups

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area at UCSF.

## 3.5 Inclusion Across the Lifespan

### 3.5.1 Age Range of Participants

Individuals ages 18 and over are eligible for this study. Children are excluded from the study because insufficient data on prospective benefits and/or adverse events for a treatment and the disease/condition is extremely rare in children

### 3.5.2 Study Design/Recruitment Considerations Related to Age Groups

The study design and recruitment strategy aim to achieve representation of age groups that reflect the demographics of the affected population

## 3.6 Duration of Treatment

All patients in this study will receive topical TXA applied to one breast intraoperatively during the study. They will only have the one exposure to the treatment at the time of surgery.

***Bilateral Mastectomy Patients***

**During surgery, after removal of breast tissue and prior to closure**

***One side Breast Skin Flap: soaked with 20ml of 25mg/ml TXA solution***

***One side Breast Skin Flap; soaked with 20ml of 0.9% normal saline (control)***

### 3.7 Duration of Follow Up

Patients are routinely followed for at least one year after undergoing post-mastectomy breast reconstruction and monitored for the development of any of the outcomes of interest and assessed for drain removal. Patients in this trial will be seen per our standard follow-up care, which typically involves a post-operative visit in the 1-4 week period, in the 5-11 week period, and some time in the 12 week to 1 year period. The exact number and schedule of visits vary by patient and their needs. Our study-specific assessment and procedures will occur at each of these regularly scheduled visits up to one year after surgery. Regarding AEs, Given the mechanism of action of TXA, there is the theoretical complication of perpetuating thrombotic events due to inhibition of clot breakdown[16]. There have been no documented events of venous thromboembolism in relation to topical administration of TXA in plastic surgery procedures, which are the most relevant to our proposed study[6, 8, 14, 15, 18]. Other side effects associated with intravenous tranexamic acid include hypersensitivity reactions, seizures, visual disturbances, and dizziness[16]. The latter three would likely not apply to our study given that with topical tranexamic acid, the drug will not cross the blood brain barrier and thus would not elicit neurologic adverse effects.

However if any patient develops these signs of symptoms, the TXA will immediately be removed from their system via washout in the operating room. If they later develop signs or symptoms of post-operative bleeding, hematoma, or seroma to their breast, they will be cared for per the standard of care which may involve aspiration, drain placement, or return to the operating room. They will not be removed from the study as these AEs are not unacceptable.

Subjects may withdraw consent at any time for any reason. A subject may be withdrawn by the investigator if enrollment into the study is determined inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

### 3.8 Primary Completion

The expected primary completion date is 2 years after the study opens to accrual, as we expect that given the volume of bilateral mastectomies performed at our institution per week, we should be able to reach at least 150 participants in 2 years.

### 3.9 Study Completion

The expected study completion date is 2 years after the study opens to accrual.

# 4 Investigational Product- TXA

Tranexamic Acid is an antifibrinolytic that is FDA approved for use in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction [16]. However, it has been used off-label with great efficacy at preventing bleeding and bruising in many other surgical fields both intravenously and topically. This study proposes the topical use of dilute TXA solution.

## 4.1 Description, Supply and Storage of Investigational Products

### 4.1.1 Tranexamic Acid

The information in the following section was obtained from the Cyklokapron (Tranexamic Acid) drug label from the FDA [16]

**Mechanism of Action**
Tranexamic acid is a synthetic lysine amino acid derivative, which diminishes the dissolution of hemostatic fibrin by plasmin. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure.
The antifibrinolytic effects of tranexamic acid are mediated by reversible interactions at multiple binding sites within plasminogen. Native human plasminogen contains 4 to 5 lysine binding sites with low affinity for tranexamic acid ($K_d$ = 750 µmol/l) and 1 with high affinity ($K_d$ = 1.1 µmol/L). The high affinity lysine site of plasminogen is involved in its binding to fibrin. Saturation of the high affinity binding site with tranexamic acid displaces plasminogen from the surface of fibrin. Although plasmin may be formed by conformational changes in plasminogen, binding to and dissolution of the fibrin matrix is inhibited.

**Metabolism**
*Distribution*
The initial volume of distribution is about 9 to 12 liters. The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin.
*Elimination*
After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal elimination phase.
*Excretion*
Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110 to 116 mL/min) and more than 95% of the dose is excreted in the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg body weight.

**Contraindications**

- In patients with subarachnoid hemorrhage, due to risk of cerebral edema and cerebral infarction
- In patients with active intravascular clotting
- In patients with severe hypersensitivity reactions to tranexamic acid or any of the ingredients (4).

**Formulation, Appearance, Packaging, and Labeling**
Tranexamic Acid is available as a single-dose 1g vial that needs to be reconstituted in 1ml of saline, to thus be 1000mg/ml. This 1g vial is readily available in the anesthesia cart in the operating room. This can then be added to 40cc saline to dilute it to 25mg/ml TXA solution. 20cc of this can then be infiltrated into the breast pocket, for a maximum exposure of 500mg of TXA to any one side

**Availability**
Tranexamic Acid is readily available at UCSF and stocked in most anesthesia carts in the operating room for perioperative administration in other surgical specialties.

**Side Effects**
The following side effects apply to intravenous systemic dosage of TXA, and may not necessarily apply to topical application.

- Thromboembolic Risk
- Seizures
- Hypersensitivity Reactions
- Visual Disturbances
- Dizziness

## 5 Treatment Plan

### 5.1 Dosage and Administration

Treatment will be administered in the operating room at the time of surgery. 20ml of 25mg/ml solution of TXA will be infiltrated into one of the breast pockets and allowed to dwell in the pocket prior to closure. The other side will receive 20ml of plain 0.9% Saline. This will be the only administration of TXA for the duration of the study.

## 5.2 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

# 6 Study Procedures and Schedule of Events

### 6.1 Study Calendar

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – [redacted]

| Period/Procedure | Screening Period | | | Assessment Period[3] | | |
|---|---|---|---|---|---|---|
| **Study Day/Visit Day** | **Pre-operative period** | **Day of Surgery** | **During Surgery** | **1-4 weeks** | **5-11 weeks** | **12 weeks – 1 year** |
| **Informed consent[1]** | **X** | | | | | |
| **Baseline conditions** | **X** | | | | | |
| **TXA Exposure** | | | | | | |
| **Right Breast** | | | | | | |
| **Left Breast** | | | **X** | | | |
| **Clinical procedures** | | | | | | |
| **Physical exam** | | **X** | **X** | **X** | **X** | **X** |
| **Vital signs** | | **X** | **X** | **X** | **X** | **X** |
| **Medical history** | | **X** | | | | |
| **AE assessment** | | | **X** | **X** | **X** | **X** |
| **Outcomes assessment[2]** | | | | **X** | **X** | **X** |

[1] Informed consent can occur prior to screening window
[2] Outcomes from clinical exam including hematoma, seroma, infection
[3] Patients are scheduled for regular clinic visits up to one year after surgery. Study-specific assessments and procedures will occur at these regularly scheduled visits. The exact timing of these visits varies by patient. If patients have multiple visits scheduled within these assessment windows, study-specific assessments and procedures may be performed at multiple visits on an optional basis

## 6.2 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

## 6.3 Schedule of Procedures and Assessments

The study-specific assessments are detailed in this section. All on-site visit procedures are allowed a window of ± 10 days unless otherwise noted.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

### *Pre-operative period*

The pre-operative period will be defined as the time between a new patient visit to plastic surgery up to and including the day of surgery. After informed consent has been obtained and during this period of time, patients will be screened for participation in the study via review of their medical record.

### *Day of surgery*

On the day of surgery, patients will undergo a condition-specific physical exam, have vital signs taken, and have their medical history reviewed.

### *Screening period*

The screening period encompasses the pre-operative period up until the day of surgery. The allowable screening window is 6 months prior to the date of surgery. Patients who do not have surgery scheduled within 6 months of screening will be re-screened for eligibility within the screening window.

### *Intraoperatively at time of bilateral mastectomy*

Tranexamic Acid is available as a sterile, single-dose 1g vial that needs to be reconstituted in 1ml of saline, to thus be 1000mg/ml. This 1g vial is readily available in the anesthesia cart in the operating room. Preoperatively, the surgery team will mix this into 40ml of 0.9% Normal Saline to thus produce a 25mg/ml TXA solution. 20ml of this will be passed onto the sterile surgical field for application to one breast pocket at the end of the case prior to closure. 20ml of 0.9% normal saline will also be passed onto the sterile surgical field for use on the control side.

The surgeon will mix the TXA solution and pass onto the surgical field as outlined above. After the completion of the bilateral mastectomy, the plastic surgeon will perform their portion of the procedure. After obtaining hemostasis and irrigating as per standard practice, they shall not use any other hemostatic agents. Immediately prior to final closure, 20ml of 25mg/ml TXA solution shall be infiltrated into the right breast pocket. 20ml of 0.9% normal saline shall be infiltrated into the left pocket. The sidedness of the TXA administration will be documented by the surgery team in our record but kept confidential from the surgery clinic staff to prevent bias at post-operative assessments. The solutions will be allowed to dwell, and JP drains will be kept off bulb suction until the end of the case. Post-procedure, each patient will be provided with standard post-operative instructions which will include a chart to record drain outputs daily for the right and left sides.

***Post-Operative Clinic Visits***

Drain output will be assessed at each clinic visit to determine timing for removal. Drains will be removed per standard practice at our institution which is when they have produced < 30cc/day for at least 3 days.

At each clinic visits up to one year after surgery, we will assess for clinical signs of hematoma, seroma, and ecchymoses. The number of post-operative clinic visits and their timings will vary by patient. Patients will be managed for hematoma and seroma as per standard procedure, whether with ultrasound, clinic aspiration, IR drain placement, or return to the operating room as deemed necessary by the senior surgeon.

***Optional Segments***

If patients have multiple visits within each block of the assessment period (1-4 weeks, 5-11 weeks, and 12 week – 1 year), study-specific assessments and procedures may be performed.

## 7 Reporting and Documentation of Results

### 7.1 Statistical analysis

We will compile an encrypted record of each patient and the study or control solution that was administered to each breast intraoperatively. We will then record data from the condition-specific physical examination at each post-operative clinic visit to track presence of hematoma, presence of seroma, laterality with worse bruising, amount of drain output prior to removal, and number of days with drain prior to removal. Demographic and surgical details will be collected for each patient. These will include patient demographics (i.e., age, BMI, race, ethnicity), clinical cancer characteristics (i.e., type of cancer, neoadjuvant chemo or radiation, adjuvant chemo or radiation), and post-operative outcomes (i.e., hematoma, seroma, infection, return to the operating room, radiology aspiration or drain placement, clinic aspiration. Results will be analyzed comparing the outcomes of the TXA treated breasts with the Control (Saline) treated breasts using T test for continuous variables, and Chi Squared for categorical variables.

Multivariate regression analysis will also be utilized to assess for the importance of various clinical and demographic factors (BMI, cancer laterality, etc.) on overall outcomes. For ecchymosis, the prevalence of worse ecchymosis with or without TXA will be reported as rated by the provider and patient at post operative visits.

### 7.2 Safety Analysis

Safety will be assessed by clinically assessing for signs of intolerance or irritation after administration of the TXA. If there are any immediate adverse effects noted related to sensitivity reactions, the JP drain will be placed to suction and the TXA solution removed and washed out via infiltration of plain saline to the breast pocket. We will assess patients at each post-operative visit with condition-specific physical exam and history to make sure there are no other adverse effects noted. If any thrombotic complications are found with no other explanation, we will deem the study unsafe and stop the study.

## 8 Study Management

### 8.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements. Before initiating this study, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

### 8.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (UCSF Institutional Review Board). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review and Monitoring Committee (PRMC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

### 8.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form 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.

### 8.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRMC and the IRB prior to implementation.
If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

### 8.5 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the administration of the study and control substance intraoperatively. The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the study. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
Study documentation includes all CRFs, data correction forms or queries, source documents, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study

## 9 Safety Parameters

### 9.1 Definitions

#### 9.1.1 Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

#### 9.1.2 Serious Adverse Event (SAE)

An adverse event is considered *serious* if, in the view of either the investigator or Sponsor-Investigator, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
    - An adverse event is considered life-threatening if, in the view of either the investigator or Sponsor-Investigator, its occurrence places the participant at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 9.1.3 Unanticipated Problem (UP)

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being study;

2) related or possibly related to participation in the research; and

3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

## 9.2 Classification of Adverse Events

### 9.2.1 Severity

Adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) version 5.0.

### 9.2.2 Attribution

Adverse events are given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- Definite – The adverse event is clearly related to the investigational agent(s) or study procedure.

- Probable – The adverse event is likely related to the investigational agent(s) or study procedure.
- Possible – The adverse event may be related to the investigational agent(s) or study procedure.
- Unrelated – the adverse event is clearly not related to the investigational agent(s) or study procedure.

### 9.2.3 Expectedness

An adverse event is considered unexpected if the nature, severity, or frequency of the event is not listed in the study protocol, product inserts, investigator brochure or informed consent document.

## 9.3 Recording of Adverse Events

Refer to the Data and Safety Monitoring Plan, located in Appendix 1.

Note: Edema and ecchymosis are part of the normal post-operative recovery process and therefore not considered adverse events unless they are Grade 3 or above, which would then be tracked and recorded in OnCore.

## 9.4 Expedited Reporting

### 9.4.1 Reporting to the HDFCCC Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the UCSF PI or his/her designee must notify the DSMC Chair (or Vice Chair) within 1 business day of knowledge of the event.

### 9.4.2 Reporting to Institutional Review Board

The UCSF PI must report events to the IRB according to institutional guidelines.

### 9.4.3 Expedited Reporting to the FDA

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

### 9.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator. For selected adverse events for which administration of the study drug/intervention was stopped, a re-challenge of the subject with the study drug/intervention may be conducted if considered both safe and ethical by the investigator.

### 9.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 1. [redacted].

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## Appendix 1 (Single Site): Phase II or III Institutional Trial

## Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

### 1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

### 2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on an annual basis, with all data from 20% percent of the enrolled participants audited by the DSMC Monitor/Auditor.

The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

## 3. Review and Oversight Requirements

### 3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** –clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

### 3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

  * A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE

will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

### 3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

**Data and Safety Monitoring Committee Contacts:**

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158