A Randomized Control Trial Assessing the Effect of Topical Tranexamic Acid on Risk of Hematoma in Breast Surgery

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PROTOCOL TITLE
A Randomized Control Trial Assessing the Effect of Topical Tranexamic Acid on Risk of Hematoma in Breast Surgery

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Investigational Agent(s)/How supplied:
Drug name: Tranexamic Acid
Pharmaceutical company name: Apollo Pharmaceuticals USA Inc.

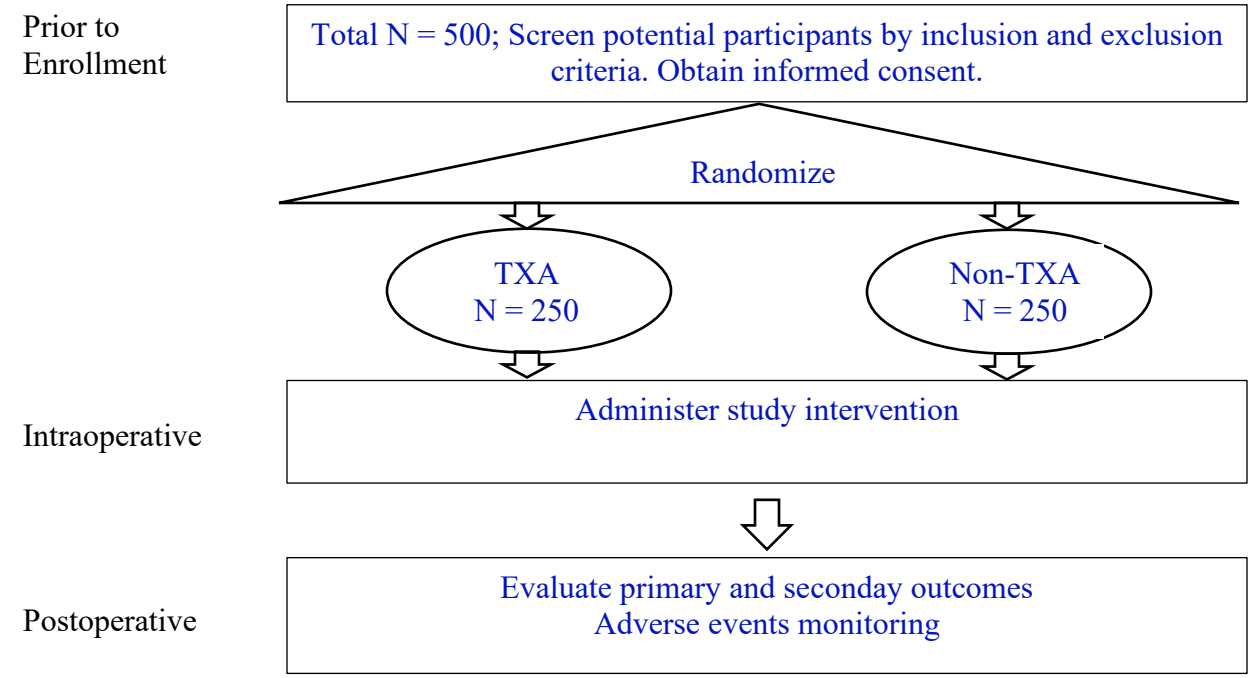
ABBREVIATIONS

AE	Adverse Event
CTSU	Clinical Traisl Support Unit
IRB	Institutional Review Board
IV	Intravenously
PI	Pincipal Investigator
SAE	Serious Adverse Event
TXA	Tranexamic Acid
UaP	Unanticipated Problem

STUDY SYNOPSIS

Title	A Randomized Control Trial Assessing the Effect of Topical Tranexamic Acid on Risk of Hematoma in Breast Surgery
Phase	Phase IV; Feasibility study
Study Design	Single blind Randomized
Study Duration	Enrollment duration: 24 months Subject follow-up duration: 4 weeks Overall study duration: 30 months
Study Center(s)	Single-center
Objectives	Evaluate the safety and efficacy of topical tranexamic acid use in preventing hematomas in routine breast plastic surgery operations
Number of Subjects	500
Disease/condition	Incidence of hematoma occurance following breast surgeries
Inclusion/Exclusion Criteria	Inclusion Criteria • Patients aged 18 or over who are undergoing bilateral breast reduction or bilateral gender-affirming mastectomy • For patients undergoing bilateral breast reduction, any skin incision pattern or pedicle is acceptable • For patients undergoing bilateral gender-affirming mastectomy, any skin incision and mastectomy type is acceptable Exclusion Criteria • Active thromboembolic disease or history of intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion • Current use of systemic anticoagulation • Hypersensitivity to tranexamic acid • Concomitant use of combined hormonal contraceptives • Use of factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid • History of acquired defective color vision • History of subarachnoid hemorrhage • Pregnancy • History of renal impairment or serum Cr$\geq$1.5mg/dL
Description of Study Intervention	Patients undergoing breast reduction surgery or gender affirming mastectomy will be randomized to received intraoperative topical TXA irrigation vs no topical TXA irrigation. The patient will be followed for 4 weeks postoperatively and the incidence of hematoma will be studied.
Duration of Intervention	Once intraoperatively
Statistical Methodology	Descriptive statistics of demographics and clinical characteristics of patients will be collected. The primary and secondary outcome will be presented as frequency counts and percentages and analyzed using Fisher's exact test.

STUDY SCHEMA



1.0 BACKGROUND AND RATIONALE

Reduction mammoplasty and gender-affirming mastectomy are two common plastic surgery operations that are generally performed in relatively healthy patients in the outpatient setting. Although these procedures are relatively safe and have a low complication profile, reoperations can occur due to hematomas[1-2]. The reported incidences of hematoma following reduction mammoplasty and gender-affirming mastectomy are around 3%-9% and 5%-10%, respectively[3-4]. Most clinically significant hematoma will require operative washout or aspiration. If left untreated, hematomas can lead to nipple necrosis and skin flap compromise which can negatively impact patient satisfaction and aesthetic outcome.

Tranexamic acid (TXA) has emerged over the past decade as an adjunctive pharmacologic agent to reduce intraoperative blood loss and prevent post-operative bleeding. Its mechanism involves inhibition of the conversion of plasminogen to plasmin which then prevents the breakdown of fibrin clots. The efficacy of tranexamic acid has been demonstrated in cardiac surgery, orthopedic surgery, spine surgery[5-10]. However, the use of tranexamic acid has not been routinely adapted into plastic surgery practice. There have been some studies assessing the use of tranexamic acid in plastic surgery procedures, including facial aesthetic surgery, craniofacial surgery, and breast reconstruction[11-17]. In addition, the route of administration can include intravenous, oral, or topical. Some believe that the topical use of tranexamic acid provides a direct hemostatic benefit during surgery while decreasing systemic absorption[14]. The concentration of topical tranexamic acid has been reported from 1.5% to 3% in orthopedic surgery and aesthetic surgery[14]. Currently, the data suggests that tranexamic acid decreases intraoperative blood loss, postoperative bruising, and surgical drain output[11-14]. However, there is a paucity of randomized prospective data on the efficacy of topical tranexamic acid in reducing clinically significant reoperative hematomas in breast surgeries.

This is a randomized control trial evaluating the efficacy of intraoperative topical tranexamic acid use in reduction mammoplasty and gender-affirming mastectomy. The primary outcome measure is the incidence of hematomas requiring operative intervention or aspiration. Secondarily, the occurrence of major thromboembolic events and other major complications will be assessed. This study hopes to further elucidate the safety and efficacy of topical tranexamic acid use in routine breast plastic surgery operations.

2.0 STUDY DESIGN, OBJECTIVES AND OUTCOME MEASURES

2.1 Primary Objectives

To evaluate the safety and efficacy of topical tranexamic acid use in preventing hematomas in routine breast plastic surgery operations

Primary Outcome Measure:

1. Incidence of hematoma requiring operative intervention

2.2 Secondary Objectives

To assess the safety profile of topical tranexamic acid when used as an intraoperative surgical irrigation

Seconary Outcome Measure:

1. Number of subjects experienging major thromboembolic events related to the study drug
2. Number of subjectrs experiencing major complicatiosn other than hematoma

3.0 SUBJECT ELIGIBILITY

Subjects must meet all of the selection criteria to be enrolled to the study. Study treatment may not begin until a subject has been consented and meets the eligibility criteria.

3.1 Inclusion Criteria

- Patients aged 18 or over who are undergoing bilateral breast reduction or bilateral gender-affirming mastectomy
- For patients undergoing bilateral breast reduction, any skin incision pattern or pedicle is acceptable
- For patients undergoing bilateral gender-affirming mastectomy, any skin incision and mastectomy type is acceptable
- Subjects must be able to understand/read/speak English

3.2 Exclusion Criteria

- Active thromboembolic disease or history of intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion
- Current use of systemic anticoagulation
- Hypersensitivity to tranexamic acid
- Concomitant use of combined hormonal contraceptives
- Use of factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid
- History of acquired defective color vision
- History of subarachnoid hemorrhage
- Pregnancy
- History of renal impairment or serum Cr$\geq$1.5mg/dL

4.0 SUBJECT SCREENING, ENROLMENT, AND RECRUITMENT

4.1 Patient Screening and Recruitment

Once a patient has been scheduled for either breast reduction or gender-affirming mastectomy, a member of the study team will conduct screening based on eligibility criteria and contact the patient using an IRB approved recruitment script to discuss the study and participation. Initial contact will either be made remotely, using the phone

number or email address listed in MiChart or a message via the patient portal, or if time allows, in-person following the consultation in a private area. If they agree to participate, they will be asked to sign an electronic consent form. Hard copies of the consent document will be available also.

4.2 Randomization

Patients will be randomized in a 1:1 ratio to either the TXA arm or the non-TXA arm. Randomization will occur pre-operatively in REDCap, the study's data management system.

4.3 Blinding

This study will be single-blinded. Patients will be blinded to the treatment. The surgical team will not be blinded.

5.0 TREATMENT PLAN

5.1 Drug dministration plan

The surgical procedure will be performed according to standard practice determined by each individual surgeon. Topical TXA will be administered intraoperatively as a surgical irrigation. For patients randomized to the TXA arm, the breast pockets will additionally be irrigated with 150 cc of 2.67% TXA (75 cc in each breast). The TXA solution will be allowed to be sit in the breast pocket for 15 minutes and then removed after 15 minutes. In the non-TXA arm, breast pockets will not receive additional irrigation.

Table 1. Drug Administration Plan

Agent	Dose	Route	Schedule
Tranexamic Acid	Total dose: 150 cc of 2.67% TXA Dose per breast: 75 cc of 2.67% TXA	Topical	Administer once intraoperative as a surgical irrigation

5.2 Toxicities and Dosing Delays/Dose Modifications

Each subject will be assessed for the development of toxicity according to the Time and Events Table (Section 6.3).

5.3 Concomitant Medications/Treatments

Concomitant drugs and/or treatments that are prohibited including the following:

- Concomitant use of systemic anticoagulation
- Concomitant use of combined hormonal contraceptives
- Concomitant use of factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid

5.4 Duration of Therapy

The study drug will be administered once intraoperatively with a total duration of 15 minutes.

Administration of treatment may continue unless one of the following criteria apply:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject voluntarily withdraws from treatment OR
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator

5.5 Off Treatment Criteria

Subjects will be removed from protocol therapy when any of the criteria listed in Section 5.4 apply. Subjects who discontinue treatment will continue protocol specific follow-up procedures as outlined in Section 5.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.6 Duration of Follow-Up

Patients will be followed for 4 weeks postoperatively. The follow-up timeline will be dictated by each surgeon's standard practice, but will generally consist of 2 visits, one approximately 1 week after surgery and a second approximately 4 weeks after surgery.

5.7 Off Study Criteria

Subjects can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

1. Subject withdraws consent (termination of treatment and follow-up);
2. Loss of ability to freely provide consent through imprisonment;
3. Subject is unable to comply with protocol requirements;
4. Treating physician judges that continuation on the study would not be in the subject's best interest;
5. Subject becomes pregnant;
6. Lost to Follow-up. If a research subject cannot be located for 1 year, the subject may be considered "lost to follow-up." All attempts to contact the subject during the one year must be documented;
7. Termination of the study by the investigators or the University of Michigan
8. Subject completes protocol treatment and follow-up criteria.

5.8 Subject Replacement

The subjects will not be replaced.

6.0 STUDY PROCEDURES AND EFFICACY ASSESSMENT

6.1 Study Procedures and Efficacy Assessments

Surgical technique

Patients will undergo their breast reduction surgery or gender-affirming mastectomy based on standard surgical technique by each surgeon. For patients undergoing breast reduction, there are no requirements on the method of skin incisions or type of pedicle used. This decision will be per individual surgeon judgement. For patients undergoing gender-affirming mastectomy, there are also no requirements on the method of skin incision and type of mastectomy. This will be per individual surgeon judgement. Once the surgeon has completed resecting the breast tissue, the weight of the resected tissue will be recorded. Hemostasis will be achieved in the standard fashion using electrocautery and the surgical sites may be irrigated according to each surgeon's preference. Next, for patient randomized to the TXA arms, the breast pockets will additionally be irrigated with 150 cc of 2.67% TXA (75 cc in each breast). The TXA solution will be allowed to be sit in the breast pocket for 15 minutes and then removed after 15 minutes. In the non-TXA arm, each breast pocket will not receive additional irrigation. The surgical sites will then be closed in a fashion that is determined by the individual surgeon. The use of postoperative drains and surgical compression garment will also be per the individual surgeon.

Follow-up

Patients will be followed for 4 weeks postoperatively. The follow-up timeline will be dictated by each surgeon’s standard practice, but will generally consist of 2 visits, one approximately 1 week after surgery and a second approximately 4 weeks after surgery. The primary and secondary outcomes of the study will be collected by a study team member via chart review.

Any adverse events will also be collected up to 30 days after surgery. Adverse events include the following:

- Hematoma
- Seroma
- Re-operation
- Infection
- Wound dehiscence
- Skin necrosis
- Rash
- Thromboembolic events (DVT, PE)
- Hypersensitivity reaction
- Seizures
- Vision change

6.2 Safety/Tolerability

Analyses will be performed for all subjects having received the study drug (See Section 8.0).

6.3 Time and Events Table

Study Element	Pre-Op	Day of Surgery	Post-op (until 4 weeks after surgery)
Informed Consent	X		
Demographics	X		
Eligibility	X		
BMI	X		
Comorbidities	X		
Smoking status	X		
Study intervention		X	
Resection weight(s)		X	
Surgical technique (including incision type and pedicle type)		X	
Use of surgical drains		X	
Estimated blood loss		X	
Need for transfusion		X	
Use of postoperative compression wrap or garments		X	X
Surgical complications		X	X
Adverse events		X	X

7.0 ADVERSE EVENTS

7.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment or intervention through 30 days after the last dose of study treatment or intervention. Any serious adverse event that occurs more than 30 days after the last study treatment or intervention and is considered related to the study treatment or intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment or intervention for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal

investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration or intervention is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration or intervention through 30 days following the last dose of the study treatment or study intervention must be recorded as an adverse event in the subject's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the subject begins study treatment or intervention is also considered an adverse event.

Review of AE and SAE data will be performed on a routine basis by the study team.

7.2 Definitions

7.2.1 Adverse Event

Adverse Event Definition
An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

7.2.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of either the investigator,its occurrence places the subject 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 for > 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

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

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the subject's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

7.2.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 8.1 for the list of expected adverse events related to the drug under study.

7.2.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

7.3 Adverse Event Characteristics

7.3.1 Terms and Grading

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

7.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE is clearly related to the study treatment/intervention.
Probable – The AE is likely related to the study treatment/intervention.
Possible – The AE may be related to the study treatment/intervention.
Unlikely – The AE is doubtfully related to the study treatment/intervention.
Unrelated – The AE is clearly NOT related to the study treatment/intervention.

7.4 Serious Adverse Event Reporting Guidelines

7.4.1 The Principal Investigator must be notified within 7 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment/intervention.

7.4.2 The investigator must report all events meeting the criteria and definition of a serious adverse event as per the local IRB reporting requirements.

7.5 Reporting of Unanticipated Problems

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), an unanticipated problem is defined as a serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol (such as revising inclusion/exclusion criteria or including a new monitoring requirement), informed consent or investigator's brochure).

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience, or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
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 than was previously known or recognized.

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to the IRB.

8.0 DRUG INFORMATION

8.1 Tranexamic Acid (TXA)

See following link to drug insert for more details:
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=a30cd382-4e2a-428d-a6d1-a530f4d230c1&type=display

- Manufacturer: Apollo Pharmaceuticals USA Inc.

- Route of administration: The drug use for this study is approved for IV use. The drug will be used topically for this study.

- Mode of action: TXA inhibits of the conversion of plasminogen to plasmin which then prevents the breakdown of fibrin clots.

- Pharmacokinetics:

    - Distribution: The initial volume of distribution is about 9-12 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 bin to serum albumin.

- Elimination: After an IV dose of 1 g of TXA, the plasma concentration time curve shows a triexponential decay with half-life of about 2 hours for the terminal elimination phase.

- Excretion: Urinary excretion is the main route elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110-116 mL/min), and more than 95% of the dose is excreted in the urine as unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after IV administration of 10 mg/kg body weight.

- Contraindications: Subarachnoid hemorrhage, active intravascular clotting

- Potential Side Effects: Thromboembolic events, seizures, hypersensitivity reactions, visual disturbances, dizziness

- Drug Interactions: No studies of interactions beteen tranexamic acid and other drugs have been conducted.

- Storage and Stability: Store at 20 C to 25 C

- Preparation Dispensing, and Labeling:
  The TXA solution will be prepared by the University of Michigan OR pharmacy.
  The drug will be prepared according to the following table.

	Concentration	Volume
Tranexamic acid	100 mg/ml	40 ml
Sodium chloride	0.9%	110 ml
Final	4000 mg/150 ml	150 ml

  The prepared solution is to be used within 6 hours on the same day of the preparation.

- Availability: Commercially available

- Return and Retention of Study Drug: The remaining/expired/used or returned drug is to be destroyed on site. The drug destruction is according to the institution standard operating procedure for drug destruction

- Drug Accountability: The University of Michigan OR Pharmacy will be providing the drug and managing the drug supply according to the institution stanard operating procedures.

9.0 STATISTICAL CONSIDERATIONS

Sample size calculation was performed for a 50% reduction in hematoma requiring operative intervention or aspiration. The study would have 80 percent power to detect the expected 50 percent risk reduction (assuming $\alpha = 0.05$, $\beta = 0.20$, n1:n2 of 1:1) if 250 patients are enrolled in each cohort.

Descriptive statistics of demographics and clinical characteristic of patients will be calculated. The descriptive statistics will be compared between the two treatment arms to assess any obvious imbalance in risk factors, despite the use of randomization.

A primary goal of the study is to evaluate the rate of hematoma requiring operation washout or aspiration in patients who receive topical TXA versus patients who do not receive topical TXA intraoperatively during breast reduction or gender-affirming mastectomy. This data will be presented as frequency counts and percentages and analyzed using Fisher's exact test. A value of $p < 0.05$ is considered statistically significant.

10.0 DATA AND SAFETY MONITORING

The study team is required to meet at least quarterly to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

11.0 REGULATORY

11.1 Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed and approved by a properly constituted IRB. Any amendments to the protocol must be reviewed and approved by the IRB.

11.2 Subject Information and Consent

Study team member will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the

study, mentioning that the subject could not read or sign the documents. No subject can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

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