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A Randomized, Single-Blinded, Placebo-Controlled Study Evaluating Postoperative Non-Opioid Pain Management Utilizing Local Anesthetics Coupled with Modulated Coagulation

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NYULMC Study Number:	S20-01420
Funding Sponsor:	Hansjorg Wyss Department of Plastic Surgery
Study Product:	Thrombin Tranexamic acid Aminocaproic acid Lidocaine Bupivacaine

Version: February 25, 2021

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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PAIN LOGS WILL BE COLLECTED FROM PARTICIPANTS WHO HAVE NOT ALREADY RETURNED THEM TO STUDY STAFF. THE PARTICIPANTS WILL BE RELEASED OF THEIR DUTIES TO THE STUDY ONCE THE LOG BOOKS HAVE BEEN RETURNED TO THE PHYSICIANS. THEY WILL

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

ε-Ahx	Aminocaproic acid
TXA	Tranexamic acid

Protocol Summary

Title	**A Randomized, Single-Blinded, Placebo-Controlled Study Evaluating Postoperative Non-Opioid Pain Management Utilizing Local Anesthetics Coupled with Modulated Coagulation**
Brief Summary	This study is a prospective randomized trial examining the effect of tranexamic acid (TXA) and aminocaproic acid (ε-Ahx) with local anesthetics and thrombin in all electively created surgical wound beds in hand surgery to provide long term pain relief and decrease the use of postoperative narcotics. All surgical created wounds for any hand surgery will be treated in a randomized fashion with the following four arms: 1. Bupivacaine + lidocaine 2. Bupivacaine + lidocaine + thrombin 3. Bupivacaine + lidocaine + thrombin + transexamic acid 4. Bupivacaine + lidocaine + thrombin + aminocaproic acid All are applied topically to surgical bed prior to closure of skin.
Phase	N/A
Objectives	The primary objective of this study is to evaluate the effectiveness of topical antifibrinolytics, thrombin and local anesthetics on postoperative pain control in patients undergoing elective hand surgery. We want to determine the efficacy of this treatment over treatment with thrombin and local anesthetics and just local anesthetics alone to the same population of patients. The secondary objective of the study is to reduce the amount of opioid pain medications required postoperatively for routine hand surgery procedures.
Methodology	Prospective single blinded study
Endpoint	Degree of pain and amount of adjuvant pain medication used at 1 month post surgery
Study Duration	12 months
Participant Duration	Pre-operative visit occurs up to 3 months prior to surgery Final Study visit occurs up to 6 weeks after surgery. Primary endpoint (returning completed pain diary to study staff) occurs at Day 14. Participants remain enrolled in the study up until their standard of care post-op visit, which typically occurs 4-6 weeks after surgery. Participation is complete when participants complete their final standard of care post-op visit.
Duration of IP administration	Applied topically to surgical bed prior to closure of skin
Population	Nontraumatic, elective upper extremity (hand) surgery cases, age 18 or older
Study Sites	NYU Langone Health Bellevue Hospital Center
Number of participants	40 (10 per study arm)
Description of Study Agent/Procedure	Applied topically to surgical bed prior to closure of skin: 1. Bupivacaine + lidocaine (reference therapy) 2. Bupivacaine + lidocaine + thrombin 3. Bupivacaine + lidocaine + thrombin + transexamic acid 4. Bupivacaine + lidocaine + thrombin + aminocaproic acid
Reference Therapy	All study agents have been used as standard of care

Statistical Analysis	To evaluate PACU time as a function of each group, a one way analysis of variance test followed by a Tukey-Kramer post hoc test will be performed. To assess the number of pain pills need as a function of each group, a Kruskal-Wallis test followed by a Dunn post hoc analysis will be performed.

Schematic of Study Design

Screening/Baseline Visit (up to 3 months prior to day of surgery)

1. Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
2. Review medical history to determine eligibility based on inclusion/exclusion criteria.
3. Review medications history to determine eligibility based on inclusion/exclusion criteria.
4. Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
5. Schedule day of surgery where primary intervention will be performed.
6. Provide participants with information regarding transexamic acid, and operative steps for administration of drugs into surgical wound prior to closure.
7. Provide participants with log books.
8. Randomize patient using sealed envelope method.

Day of Surgery

1. Verify patient still meets inclusion/exclusion criteria.
2. Administer study treatment
3. Patient fills out Day 1 of pain diary

Intermediate Visits

1. Participants will be called via phone each day by the study team to ensure they have completed their daily log of numerical pain rating scale and number of pain pills taken.
2. They will arrive for an intermediate visit on their first postoperative visit (variable time, between 3-14 days postoperatively). Log books will be collected only after postoperative day 14.

Final Study Visit (up to 6 weeks post surgery)

Pain logs will be collected from participants who have not already returned them to study staff. The participants will be released of their duties to the study once the log books have been returned to the physicians. They will continue their routine follow up per the follow up schedule for each hand surgery procedure. No additional data is collected for study purposes at post-op visits beyond data collected per standard of care.

1 Key Roles

Principal Investigator	David Chiu, MD Professor, Hansjorg Wyss Department of Plastic Surgery at NYU Grossman School of Medicine Professor, Department of Neurosurgery at NYU Grossman School of Medicine Chief Hand Surgery 900 Park Avenue New York, NY 10021 David.Chiu@nyulangone.org 212-879-8880
Sub-Investigators	Jing Bai Qin, MD Hansjorg Wyss Department of Plastic Surgery 222 E. 41st St. 6th Fl. New York, NY 10017 Baijing.Qin@nyulangone.org 212-879-8880 Anna Steve, MD Hansjorg Wyss Department of Plastic Surgery 222 E. 41st St. 6th Fl. New York, NY 10017 Anna.Steve@nyulangone.org 646-799-4630

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Opioid pain medication use and its abuse has been an epidemic in the United States for greater than the past decade. It has been shown that for the past decade and greater, the prescribing patterns for opioid pain medications have drastically changed; however, are still relatively high compared to 1999. 6 It has been also shown that many physicians prescribe an excessive amount of opioids to patients undergoing elective upper extremity surgeries.

This study aims to potentially minimize the use of opioid pain medication following outpatient elective hand surgery procedures. The PI of this current project has already published an article that shows the superior pain control postoperatively utilizing topical thrombin and local anesthetic. Even so, there is limited study for the use of intraoperative techniques to control post operative pain.

2.2 Name and Description of the Investigational Agent

1. **Topical lidocaine and bupivacaine alone; in this treatment group, each solution will include 5 ml of 1% lidocaine, 5 ml of 0.25% bupivacaine**
2. **Topical lidocaine and bupivacaine with thrombin; in this treatment group, each solution will include 5 ml of 1% lidocaine, 5 ml of 0.25% bupivacaine, 10000 units of thrombin**
3. **Topical lidocaine and bupivacaine with thrombin and tranexamic acid; in this treatment group, each solution will include 5 ml of 1% lidocaine, 5 ml of 0.25% bupivacaine, 10000 units of thrombin, and 500 mg of tranexamic acid**
4. **Topical lidocaine and bupivacaine with thrombin and aminocaproic acid; in this treatment group, each solution will include 5 ml of 1% lidocaine, 5 ml of 0.25% bupivacaine, 10000 units of thrombin, and 1000 mg of aminocaproic acid**

Tranexamic acid:

FDA-approved usage for intravenous tranexamic acid (TXA) is for heavy menstrual bleeding and short-term prevention in patients with hemophilia.

We plan on using a total dose of 500 mg (20 mL) total for each case.

Aminocaproic acid:
FDA notes that aminocaproic acid is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. Aminocaproic acid inhibits both the action of plasminogen activators and to a lesser degree, plasmin activity. The fibrinolysis-inhibitory effects of aminocaproic acid appear to be exerted principally via inhibition of plasminogen activators and to a lesser degree through antiplasmin activity. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

We will use a total of 1000 mg total for each case.

Recombinant Human Thrombin:
Topical thrombin is approved by the FDA as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques is not sufficient.

Recombinant human thrombin is available as 5000-unit and 20,000-unit vials of sterile recombinant topical thrombin lyophilized powder for solution. When reconstituted as directed, the final solution contains 1000 units/mL.

For our topical application, we will use a total of 10000 units per open surgical study arm involving use of Thrombin.

Lidocaine Hydrochloride with Epinephrine:
Topical lidocaine product is approved for FDA as an amide local anesthetic in any indication for relief of pain associated with superficial minor surgery and as an adjunct for local infiltration anesthesia. It is frequently used as a standard local anesthetic for surgical procedures.

Each mL contains lidocaine hydrochloride and epinephrine, with 0.5 mg sodium metabisulfite as an antioxidant and 0.2 mg citric acid as a stabilizer.

We plan on using a total of 5 mLs per open surgical study arm involving lidocaine hydrochloride and epinephrine.

Bupivacaine Hydrochloride with Epinephrine:
Topical bupivacaine is approved for FDA as indicated for the production of local anesthesia for procedures by infiltration injection. It is frequently used as a standard local anesthetic for surgical procedures.

Each mL contains bupivacaine hydrochloride and 0.005 mg epinephrine, with 0.5 mg sodium metabisulfite as an antioxidant and 0.2 mg citric acid (anhydrous) as stabilizer.

We plan on using a total of 5 mLs per open surgical study arm involving Bupivacaine Hydrochloride with Epinephrine.

The clinical investigation of the drugs noted above is exempt from IND requirements in accordance with 21 CFR 312.2(b) because:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) As noted in section 2.2.2., the investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

The investigation is conducted in compliance with the requirements of 312.7.

2.2.1 Clinical Data to Date

Tranexamic acid is a synthetic derivative of the amino acid lysine. Its mechanism of action is via inhibition of fibrinolysis by blocking the lysine binding site on plasminogen. It acts as a competitive inhibitor of conversion of plasminogen to plasmin and at higher concentrations a non-competitive inhibitor of plasmin.

Thrombin is a serine protease coagulant that both converts soluble fibrinogen into insoluble fibrin strands and activates factor XIII to catalyse covalent crosslinking of these strands, thereby forming a stable fibrin clot. It also promotes platelet aggregation at the site of vascular injury, via the activation of specific protease-activated receptors. Thus, exogenous topical thrombin directly activates the terminal stages of blood clot formation at the site of application.

Bupivicaine is an amino-amide local anesthetic. Onset of action is 1-17 min. Duration of action (route and dose-dependent) 2-9 hr. Half life: neonates 8.1 hours, adults: 2.7 hours. Time to peak plasma concentration (for peripheral, epidural, or caudal block): 30-45 min. Protein binding: about 95%. Metabolism: hepatic. Excretion: renal (6% unchanged).

Lidocaine is an amino-amide local anesthetic. Onset of action is 2-4 min. Duration of action (route and dose-dependent) 2 - 3.5 hr. Half life: 1.5-2 hr. Protein binding: 60-80%. Metabolism: hepatic. Excretion: renal.

Previous work by our group showed that the addition of topical thrombin to local anesthetic at the end of elective hand surgery provides for sustained postoperative pain control. Patients in that study who received thrombin and local anesthetic before wound closure had lower pain levels and were discharged from the PACU sooner than those who received local anesthetic alone. We hypothesize that the addition of a topical antifibrinolytic agent such as transexamic acid with thrombin and local anesthetic at the end of elective hand surgery will provide even greater pain relief through the formation of a stable clot that prolongs the effect of local anesthesia. We hypothesize we will see even lower pain scores and lower number of pain pills and shorter PACU times in the postoperative period in the groups with a transexamic acid + thrombin + local anesthetic than the groups with just thrombin + local anesthetic.

2.2.2 Dose Rationale (if applicable)

The dosages that we use for treatment groups 1 and 2 in this research study are consistent with the dosages given per standard of care at this institution. Treatment groups 1 and 2 are considered equivalent and are both used in our practice as standard of care.

Previous literature has shown that topical application of tranexamic acid and aminocaproic acid decreases postsurgical bleeding after major surgical procedures, and that this is a promising strategy to improve surgical outcomes (Ipema H et al., Use of topical tranexamic acid or aminocaproic acid to prevent bleeding after major surgical procedures). Clinical trials, case reports, and meta-analyses describing topical use of tranexamic acid or aminocaproic acid to prevent postoperative bleeding all

showed reduction of postoperative blood loss. The dosages used in these studies are as follows: 4 trials used solutions containing tranexamic acid (1-2.5 g in 100-250 mL of 0.9% NaCl), and 1 trial assessed a solution containing aminocaproic acid (24 g in 250 mL of 0.9% NaCl).

Literature has shown that topical TXA is safe and effective for reducing perioperative blood loss. It is therefore a great agent for controlling perioperative blood loss and potentially lowers transfusion rates and shortens length of hospital stay (Wei W et al., Comparison of intravenous and topical tranexamic acid in total knee arthroplasty). Off-label use of topical TXA in surgery has demonstrated that patients who received topical TXA were associated with a shorter length of hospital stay (Teoh T et al., Prophylactic Topical Tranexamic Acid Versus Placebo in Surgical Patients A Systematic Review and Meta-Analysis*).

Tranexemic acid: We plan on using a total dose of 500 mg (20 mL) total for each case.

Aminocaproic acid: We will use a total of 1000 mg total for each case.

Recombinant Human Thrombin: For our topical application, we will use a total of 10000 units per open surgical study arm involving use of Thrombin.

Lidocaine Hydrochloride with Epinephrine: We plan on using a total of 5 mLs per open surgical study arm involving lidocaine hydrochloride and epinephrine.

Bupivacaine Hydrochloride with Epinephrine: We plan on using a total of 5 mLs per open surgical study arm involving bupivacaine hydrochloride with epinephrine.

Each study arm will receive an intraoperative local block at the site of surgery by the operative surgeon prior to incision, in accordance with our institutional standard of care..

2.3 Rationale

Pain management immediately post operatively is often difficult without utilizing opioids. With increasing concern about opioid addiction, our study hopes to elucidate other methods of immediate post operative pain control that will limit the amount of opioids taken after having elective hand surgery.

We propose that the utilization of thrombin, topical anesthetic, and an antifibrinolytic will improve post operative pain control.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Lidocaine: Tinnitus, cardiac irritability, and neurological disturbance have been noted only when patients receive more than 4mg/kg of lidocaine. In this study, we are using less than 1mg/kg, which is a lot lower than the maximum amount of medication given to patients.

Bupivacaine: Tinnitus, headache, difficulty with urination, chest discomfort, problems with speech, cardiac irritability, and neurological disturbance have been noted only when patients receive more than 3mg/kg of bupivicaine. In this study, we are using less than 1mg/kg, which is a lot lower than the maximum amount of medication given to patients.

It is well known that bupivicaine can cause adverse effects (cardiotoxicity, and central nervous system toxicity); however, the dose and route of administration in our study minimizes these risks, as noted above.

Thrombin: Major risks of thrombin have only been seen in systemic usage. We are using thrombin only topically, in order to minimize side effects that may occur when used systemically. Topical thrombin per

the FDA has risks of anaphylactic reactions that may occur in the clinical trial with similar frequency in the two study groups. The most common adverse event reported was procedural complications and pruritus. This risk is seen in patients with amide anesthetic sensitivity and we will screen patients for this preoperative and exclude patients with this potential risk.

Tranexamic acid: Major risks of tranexamic acid have only been seen in systemic usage. We are using tranexamic acid only topically, in order to minimize side effects that may occur when used systemically. For topical tranexamic acid according to the FDA, the most common adverse reactions are nausea, vomiting, diarrhea, allergic dermatitis, giddiness, hypotension, and thromboembolic events.

Aminocaproic acid: Major risks of aminocaproic acid have only been seen in systemic usage. We are using aminocaproic acid only topically, in order to minimize side effects that may occur when used systemically. For topical aminocaproic acid according to the FDA, it is generally well tolerated. The following adverse experiences have been reported: General: Edema, headache, malaise. Hypersensitivity Reactions: Allergic and anaphylactoid reactions, anaphylaxis. Cardiovascular: Bradycardia, hypotension, peripheral ischemia, thrombosis. Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting. Hematologic: Agranulocytosis, coagulation disorder, leukopenia, thrombocytopenia. Musculoskeletal: CPK increased, muscle weakness, myalgia, myopathy (see WARNINGS), myositis, rhabdomyolysis. Neurologic: Confusion, convulsions, delirium, dizziness, hallucinations, intracranial hypertension, stroke, syncope. Respiratory: Dyspnea, nasal congestion, pulmonary embolism. Skin: Pruritis, rash. Special Senses: Tinnitus, vision decreased, watery eyes. Urogenital: BUN increased, renal failure. There have been some reports of dry ejaculation during the period of AMICAR treatment. These have been reported to date only in hemophilia patients who received the drug after undergoing dental surgical procedures. However, this symptom resolved in all patients within 24 to 48 hours of completion of therapy.

2.4.2 Known Potential Benefits

If this study shows improved pain control in the immediate postoperative period, decreased opioid use by patients will be a major benefit. If this study has a proven impact on postoperative pain control without the utilization of opioid pain medication, then the number of prescription medications will be reduced thus reducing cost of filled opioid prescriptions. However, we cannot guarantee subjects will benefit directly from being in the study. It is hoped that the knowledge gained from this study will help others in the future.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective of this study is to evaluate the effectiveness of topical antifibrinolytics, thrombin and local anesthetics on postoperative pain control in patients undergoing elective hand surgery. We want to determine the efficacy of this treatment over treatment with thrombin and local anesthetics and just local anesthetics alone to the same population of patients.

3.2 Secondary Objectives (if applicable)

The secondary objective of the study is to reduce the amount of opioid pain medications required postoperatively for routine hand surgery procedures.

4 Study Design and Endpoints

4.1 Description of Study Design

The study is a single blinded placebo-controlled prospective randomized controlled trial. Patients will be randomized into one of four groups:

1. Topical lidocaine and bupivacaine alone
2. Topical lidocaine and bupivacaine with thrombin
3. Topical lidocaine and bupivacaine with thrombin and tranexamic acid

4. Topical lidocaine and bupivacaine with thrombin and aminocaproic acid

Patients meeting inclusion criteria will be randomized at their preoperative appointments and an initial evaluation will be completed for pre-operative pain levels using the numerical pain rating scale. At the conclusion of their respective surgery just prior to wound closure, the appropriate medications will be topically administered into the wound and the wound will be closed via standard method. Patients will record pain scores at home daily and also record the amount of pain pills needed postoperatively until post operative day 14. Analysis will be completed to ascertain the difference between preoperative and postoperative scales after 14 days among the four groups. We will also analyze the differences in the amount of opioid pain pills needed postoperatively among the four study groups.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Comparison of pain levels using a visual analog scale preoperatively and postoperatively

4.2.2 Secondary Study Endpoints

Number of pain pills used
Total time in PACU

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

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

1. Age 18 or older
2. Any patient undergoing elective hand surgery

5.2 Exclusion Criteria

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

1. Any patient with a traumatic open wound (only surgically created wounds will be included)
2. History of chronic pain
3. History of narcotic addiction
4. History of recreational drug dependency
5. History of psychiatric pathology
6. Allergy to local anesthetics, recombinant human thrombin or transexamic acid
7. Any patient receiving a supra/infraclavicular block for anesthesia

5.3 Vulnerable Subjects

No vulnerable populations will be included.

5.4 Strategies for Recruitment and Retention

Patients will be prospectively recruited after IRB approval until a total of 10 patients are enrolled and randomized in each study group for a total of 40 patients. We believe this process will take approximately 2-3 months.

Patients will be recruited from investigator and sub-investigator clinical practices, during each patient's pre-operative visit for elective hand surgery.

5.5 Duration of Study Participation

Pre-operative visit will occur up to 3 months prior to surgery. Final Study visit will occur up to 6 weeks after surgery. Primary endpoint (returning completed pain diary to study staff) occurs at Day 14. Participants

remain enrolled in the study up until their standard of care post-op visit, which typically occurs 4-6 weeks after surgery. Participation is complete when participants complete their final standard of care post-op visit.

5.6 Total Number of Participants and Sites

Patients will be recruited from NYU Langone Health and from Bellevue Hospital Center.

Recruitment will end when approximately 40 participants are enrolled. It is expected that approximately 40 participants will be enrolled in order to produce 40 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study investigators and to regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

1. Topical lidocaine and bupivacaine alone
2. Topical lidocaine and bupivacaine with thrombin
3. Topical lidocaine and bupivacaine with thrombin and tranexamic acid
4. Topical lidocaine and bupivacaine with thrombin and aminocaproic acid

6.1.1 Acquisition

All drugs in this study are readily available at the hospitals where the study is to be performed. Nursing staff will verify expiration date and untampered vials prior to use intraoperatively. Unused drugs will be disposed of by all proper protocols per the hospital.

6.1.2 Dosing and Administration

Tranexemic acid:
We plan on using a total dose of 500 mg (20 mL) total for each case.
Aminocaproic acid: We will use a total of 1000 mg total for each case.

Recombinant Human Thrombin:
For our topical application, we will use a total of 10000 units per open surgical study arm involving use of Thrombin.

Lidocaine Hydrochloride with Epinephrine:
We plan on using a total of 5 mLs per open surgical study arm involving lidocaine hydrochloride and epinephrine.

Bupivacaine Hydrochloride with Epinephrine:
We plan on using a total of 5 mLs per open surgical study arm involving bupivacaine hydrochloride with epinephrine.

Each study arm will receive an intraoperative local block at the site of surgery by the operative surgeon prior to incision.

6.1.3 Route of Administration

Study drugs are applied topically to surgical bed prior to closure of skin.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Patients meeting inclusion criteria will be randomized at their preoperative appointments with a sealed envelope method and an initial evaluation will be completed for pre-operative pain levels using the numerical pain rating scale. At the conclusion of their respective surgery just prior to wound closure, the appropriate medications will be topically administered into the wound and the wound will be closed via standard method. Patients will record pain scores at home daily and also record the amount of pain pills (Norco 5/325mg) needed postoperatively until post operative day 14.

Preoperative analog pain scoring will be performed followed by postoperative analog pain scoring on postoperative day 0-14. Compliance will be recorded by the patient in a written form. Number of opioid pain medications taken will also be recorded by patient in a written form.

Analog pain scoring preoperatively on day of surgery and postoperatively day of surgery. Pain scale from 0 (no pain) to 10 (highest level of pain ever experienced). This scoring system will also be utilized by the patient daily until postoperative day 14.

Opioid prescriptions (Norco 5/325 mg) will be given to patients post operatively. Total number of pills taken up until post operative day 14 will be recorded by the patient.

This will allow us to track the patients relative pain pre and postoperatively until postoperative day 14.

· Medical history will be obtained in hand surgery clinic at initial patient presentation.

· Medication history will include details about the specifics of their hand problem along with a past medical history that includes history of chronic pain, narcotic addiction, recreational drug dependency, psychiatric pathologies, allergy to drugs and preferences for anesthesia. Those patients who only wish to have an anesthetic upper extremity block performed by anesthesia will not qualify for the study.
· Physical examination will consist of a full hand examination. The most important criteria will the presence or absences of an already open wound prior to surgical intervention.
· The patients will be counseled on the study objectives and methods of data collection. The numerical pain rating scale will be explained in detail to the patient.
· The patients will be administered a pain dairy in which they will be able to log their daily pain level at the same time each day (AM) based on the numeric pain scale (1-10). They will also be instructed to log their pain medication usage and the number of pills of Norco 5/325 mg that are consumed. This log will continue daily for a total of 14 days postoperatively.

The first visit will be the initial evaluation of the patient when they present for their individual hand surgery evaluation. If they qualify for their study, an initial preoperative pain scale will be used to assess their pain level.
The next assessment will be on the day of surgery. The patient will be evaluated in the preoperative holding area and another pain level evaluation will be done for a POD#0 timepoint.
The patient will be evaluated in PACU for total time in PACU.
Each patient will receive their log book and take it home with them. The patients will be called on each day by the study team to ensure that they have been logging their daily pain score. The study team will call the patient for this purpose.
The patients will be seen in person on their first postoperative visit (approximately 1-2 weeks later). If this is prior to postoperative day 14, they will follow up again in hand clinic after day 14 (in 4-6 weeks post-surgery) to submit their log books.

7.2 Study Schedule

Screening/Baseline Visit (up to 3 months prior to day of surgery)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Schedule day of surgery where primary intervention will be performed.
- Provide participants with information regarding transexamic acid, and operative steps for administration of drugs into surgical wound prior to closure.
- Provide participants with log books.
- Randomize patient using sealed envelope method.

Day of Surgery

- Verify patient still meets inclusion/exclusion criteria.
- Administer study treatment
- Patient fills out Day 1 of pain diary

Intermediate Visits

- Participants will be called via phone each day by the study team to ensure they have completed their daily log of numerical pain rating scale and number of pain pills taken.
- They will arrive for an intermediate visit on their first postoperative visit (variable time, between 3-14 days postoperatively). Log books will be collected only after postoperative day 14.

Final Study Visit (up to 6 weeks post surgery)

Pain logs will be collected from participants who have not already returned them to study staff. The participants will be released of their duties to the study once the log books have been returned to the physicians. They will continue their routine follow up per the follow up schedule for each hand surgery procedure. No additional data is collected for study purposes at post-op visits beyond data collected per standard of care.

8 Assessment of Safety

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Unexpected AEs which are possibly related, probably related, or definitely related will be reported to the IRB using the Reportable New Information (RNI) tool within Research Navigator within 48 hours of study team awareness.

All other AEs will be documented in the AE/SAE log to be submitted to the IRB at the time of annual continuing review.

8.4.2 Serious Adverse Event Reporting

Unexpected SAEs which are possibly related, probably related, or definitely related will be reported to the IRB using the Reportable New Information (RNI) tool within Research Navigator within 48 hours of study team awareness.

All other SAEs will be documented in the AE/SAE log to be submitted to the IRB at the time of annual continuing review.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures within 24 hours of the IRB's receipt of the report of the problem from the investigator.

8.5 Study Halting Rules

Administration of study agents will be halted and the study will be discontinued if the PI determines that 3 unexpected and related (possibly related, probably related, or definitely related) AEs have occurred.

8.6 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data Safety Monitoring
The PI is responsible for conducting systematic and periodic reviews of aggregate data and adverse events in accordance with the data safety monitoring plan. In addition to reviewing AEs, the PI will review assessments of drain site, pain scores, and opioid usage in order to ensure safety of enrolled subjects.

The PI will review all study data and adverse events throughout the study on an annual basis. Administration of study agents will be halted and the study will be discontinued if the PI determines that 3 unexpected and related (possibly related, probably related, or definitely related) AEs have occurred.

A summary of the outcomes of these safety reviews along with accumulated adverse events and deviations will be submitted to the IRB as part of an annual progress report at the time of the Continuing Review submission.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Individual subject monitoring for this study will be performed by the PI in an ongoing basis as patients are undergo routine clinical follow-up assessments of their drain sites. We review these clinical assessments and add them to our study data. There are no additional assessments of safety that the patient will need to undergo as part of this study.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

10.1.1 General Approach

Each arm of this randomized, single-blinded, placebo-controlled study will have a minimum of 10 patients. There will be a minimum of 40 patients in the study. Patients will be randomized using Microsoft Excel.

Simple randomization will be used to determine the treatment arm. In order for us to power our study based on a previous similar study at NYU for topical application (Haddock et al., Thrombin and Topical Local Anesthetic for Postoperative Pain Management), we will need 10 patients for each individual treatment arm to detect any difference in the outcome.

10.1.2 Analysis of the Primary Efficacy Endpoint(s)

Data will be expressed either as a mean (SD) or median and interquartile range (IQR). To evaluate PACU time as a function of each group, a one way analysis of variance test followed by a Tukey-Kramer post hoc test will be performed. To assess the number of pain pills need as a function of each group, a Kruskal-Wallis test followed by a Dunn post hoc analysis will be performed. To compare pain levels between the treatment arms, pain scores on a scale of 1 (lowest aka no pain) to 10 (highest pain experienced in life) will be collected daily via a patient log. They will be analyzed as a change from baseline (preoperative) pain levels and analyzed used a series of two proportion z tests with a family error rate equal to 0.05. For all tests, a P value of less than 0.05 will be considered statistically significant.

Pain is a subjective measure. We will be using an analog pain scale and reference them to the patients pre and postoperatively to account for this. Patients may take over the counter pain medication postoperatively. We cannot control the patient's use of over the counter pain medications while at home, thus we will have to rely on their accuracy and honesty for this study.

Patients will be called daily to ensure completion of daily log books. If they are not able to do this, they will be removed from the study analysis. If the patients return to clinic at 4-6 weeks post-surgery and they have completed their logs, their data will still be accepted. But if there is missing data, they will be removed from the analysis.

11 Source Documents and Access to Source Data/Documents

All data will be stored on HIPAA compliant and encrypted REDCap, approved by the institution and managed by MCIT.
Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source

documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agents, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 Consent Procedures and Documentation

The informed consent process begins during the initial consultation visit for hand surgery, which is scheduled up to 3 months prior to the scheduled surgery. Informed consent can be obtained up until the day before the scheduled surgery.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management system used by NYU Langone Medical Center research staff, REDCap, will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Study data will be entered by the study team into HIPAA compliant, encrypted REDCap managed by MCIT. Patient binders containing signed ICFs and completed pain logs, as well as any other paper source documentation and/or CRFs, will be stored in a locked filing cabinet accessible only to the study team.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;

15 Study Finances

15.1 Funding Source

This study will be funded by the Hansjorg Wyss Department of Plastic Surgery.

15.2 Costs to the Participant

There are no anticipated costs to the participant associated with this study.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 References

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