Title:

TAHFT: Evaluation of **T**ranexamic **A**cid Prior to Surgery in the Geriatric **H**ip **F**racture Population for the Reduction of Post-Operative Blood **T**ransfusion

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Study Product	Tranexamic Acid (TXA)
IRB Number	*Will not be available at the time of initial submission.*

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Study Summary

Title	Evaluation of **T**ranexamic **A**cid Prior to Surgery in the Geriatric **H**ip **F**racture Population for the Reduction of Post-Operative Blood **T**ransfusion
Short Title	**TAHFT**
IRB Number	*Please note that this number will be assigned by the IRB and thus will not be in existence at the time of protocol development and initial review.*
Methodology	The overall design of the study is a prospective, double-blinded, randomized study in the geriatric hip fracture population comparing those who receive intravenous tranexamic acid prior to incision to those who receive a placebo.
Study Duration	The patient enrollment phase will take approximately 24 months. Study duration for each subject is 3 months. Total study duration is expected to be 36 months, allowing for study start-up before enrollment and data analysis and manuscript writing after completion of study follow-up.
Study Center(s)	Lancaster General Hospital
Specific aims	Primary: • To compare the percentage of subjects that receive acute post-operative transfusions in the group administered intravenous tranexamic acid compared to the group administered placebo Secondary: • To compare length of inpatient hospital stay and the percentage of subjects with readmissions with associated diagnoses within 30 days between the treatment groups • To compare rates of complications and mortality within 90 days post hip surgery between the treatment groups
Number of Subjects	The study will enroll approximately four hundred (400) qualified subjects.
Main Inclusion and Exclusion Criteria	INCLUSION - Eligible subjects will meet ALL the following criteria: 1. Written informed consent 2. Age ≥ 65 years 3. Hip fracture location within the femoral neck, intertrochanteric, and subtrochanteric regions 4. Indication for surgical intervention with one of the following: hemiarthoplasty, total hip replacement, sliding plate and screw fixation, or intramedullary fixation. EXCLUSION – Eligible subjects will NOT meet any of the following criteria: 1. Indication for closed reduction and percutaneous screw fixation 2. Allergy to tranexamic acid 3. Cerebrovascular accident/stroke, active coronary disease/myocardial infarction, or deep vein thrombosis/pulmonary emboli within one (1) month prior to the fracture 4. Presence of hypercoagulable disorder
Intervention	The intervention in the two arms consists of administration of 1) 100 cc normal saline with 1g of tranexamic acid in solution or 2) 100 cc normal saline alone.

Statistical Methodology	For assessing the primary endpoint, we will calculate an odds ratio (with a 95% confidence interval) for transfusion with p-values calculated using a likelihood ratio.
Data and Safety Monitoring	Monitoring of adverse events will occur every 6 months over the course of the study or more frequently if needed. One interim analysis is planned to assess the primary endpoint for significant efficacy sufficient to stop the trial early. The interim analysis is planned for the ¾ point of the trial or a minimum of 300 subjects enrolled.

Background and Study Rationale

1 Introduction

Geriatric hip fracture patients may significantly benefit from routine administration of tranexamic acid (TXA) prior to the procedure to decrease the risk of blood loss. Thus, this may further reduce the rate of blood transfusions and complications associated with this treatment. With the high volume of geriatric hip fractures treated at Lancaster General Hospital, we would obtain a large patient population to perform an ideal study.

1.1 Background and Relevant Literature

The geriatric hip fracture population is growing throughout the United States secondary to the aging baby boomer population. These fractures require surgical intervention for stabilization and proper rehabilitation. During the 2017 fiscal year, 420 hip fracture operations were performed at Lancaster General Hospital on the geriatric population, and this number has been increasing over the past decade. This population has a significant increase in morbidity and mortality (approximately 50%) within 1 year if the patient does not have an operation within 36 hours of the trauma.[1,2] Therefore, patients are quickly optimized to a degree where they are safe to tolerate the anesthesia and surgical procedure.

A significant portion of the geriatric hip fracture population have comorbidities including chronic kidney disease, congestive heart failure, ischemic heart disease, stroke, etc.[3] These patients may be anemic prior to the surgery, and are at increased risk for further blood loss as a result of the fracture and surgical operation.[4,5] However, intra-operative or post-operative blood transfusions also increase the risk of infectious and non-infectious complications (i.e. anaphylaxis, acute hemolytic reaction, circulatory overload, metabolic derangements, etc.), cost of admission, and length of stay in this population.[6-8] Evidence has demonstrated that postoperative cardiovascular complications are associated with anemia and blood transfusions.[9-11] Therefore, providers must be cautious and aware of risks when deciding if transfusions are indicated for this population.

Tranexamic acid (TXA) is an anti-fibrinolytic medication that has transformed total joint replacement management regarding blood loss prevention. Multiple studies have proven its effectiveness of significantly reducing blood loss during total hip and knee replacement procedures compared to placebo.[12-28] Thus, this medication has drastically reduced the need for post-operative transfusions in this patient population. However, this patient population may be optimized prior to surgery if they have significant anemia because joint replacement surgeries are generally elective and not urgent or emergent.

Geriatric patients requiring emergent hip fracture repair may significantly benefit from routine administration of TXA prior to the procedure to decrease the risk of blood loss. Thus, treatment may

further reduce the percentage of patients who experience blood transfusions and complications associated with transfusions. However, there are only a couple of studies analyzing the use of TXA in the hip fracture population, and these were underpowered.[29-31] Additionally, the American Academy of Orthopedic Surgery and American Association of Hip and Knee Surgeons released guidelines regarding the use of tranexamic acid based on existing literature and clinical evidence.[32] They stated the greatest shortcoming in the literature is the lack of high level evidence to support the use of TXA in patients with a history of VTE, myocardial infarction, cerebrovascular event, transient ischemic attack, and/or vascular stent placement. Therefore, they encourage future research to determine the safety of TXA in the high-risk patient.

With the high volume of geriatric hip fractures treated at Lancaster General Hospital (LGH), we aim to obtain a large patient population to perform an ideal study. We would examine if administration of TXA prior to incision in the geriatric hip fracture patient population decreases the risk of intra-operative or post-operative blood transfusions compared to placebo and determine the safety profile of such administration in high-risk patients.

2 Study Objectives

2.1 Primary Objective

The primary objective of the study is to determine if administration of pre-operative intravenous tranexamic acid for surgical geriatric hip fracture subjects reduces the need for post-operative blood transfusions compared to the geriatric hip fracture subjects who are administered placebo.

2.2 Secondary Objectives

A secondary objective is to determine if TXA increases the risk of complications in the geriatric hip fracture population compared to placebo. Complications may include deep vein thrombosis, pulmonary emboli, myocardial infarction, and cerebral vascular events. We also monitor for complications in subjects who do not receive the TXA. We also will look for differences between the groups in 30 day readmission rates.

3 Investigational Plan

3.1 General Design

The overall design of the study is a prospective, double-blinded, randomized study comparing the post-operative rate of blood transfusions in surgical geriatric hip fracture subjects who are administered intravenous TXA prior to incision compared to those who receive a placebo.

Data will be collected at Enrollment, Baseline, Hospital Discharge, and at Follow Up Visits at 2 (two) weeks, six (6) weeks and three (3) months in conjunction with their standard of care post-operative visits. In addition, all unscheduled visits, hospital readmissions, and deaths will also be collected at 6 weeks and 3 months post-surgery.

3.2 Allocation to Interventional Group

Consented subjects are randomized to participate in the study if they meet eligibility criteria. Subjects are randomized in a 1:1 ratio to receive either TXA (intervention), or placebo (control). The randomization will be stratified by the type of procedure:

1. Hemiarthroplasty/total hip replacement
2. Internal fixation with sliding hip screw/cephalomedullary nail

Each stratum will have its own list of random treatment assignments to promote balance in the treatment groups with respect to the stratification factors. The treatment assignments will be computer-generated in blocks of varying sizes using REDCap.

3.3 Study Measures

The following data will be collected from Epic for study purposes:

- Subject demographics (gender, age, race, BMI)
- Hospital admission and discharge dates
- Hospital admission and discharge anti-coagulation medications and fish oil utilization, etc.
- Pre-operative standard of care lab work (CBC, CMP, PT/INR, etc.)
- Type of surgical procedure performed
- Intraoperative hemoglobin/hematocrit (H/H) levels if available
- Post-operative standard of care lab work, days 1 & 2 (CBC, BMP, etc.)
- Number of transfused packed red blood cell units during peri-operative period
- Hemoglobin/hematocrit levels before and after transfusion
- Post-operative DVT prophylaxis
- Length of hospital stay for current hip fracture admission
- Readmission rates within 30 days of hip surgery along with admission diagnosis
- Complications within 90 days of surgery
- Death within 90 days of surgery along with cause of death

3.4 Study Outcomes

3.4.1 Primary Study Outcome

The primary outcome of this study is acute post-operative transfusion of packed red blood cells.

3.4.2 Secondary Study Outcomes

The secondary outcomes of this study include:

- Length of inpatient hospital stay
- Readmission within 30 days post hip surgery along with the associated readmission diagnosis
- Complications within 90 days post hip surgery
- Death within 90 days post hip surgery

4 Study Population and Duration of Participation

Subjects will be recruited from geriatric hip fracture patients acutely admitted through the Lancaster General Hospital Emergency Department and treated by OAL physicians. Consenting subjects will be followed for 90 days post-surgery. Participation ends upon the completion of the 3-month post-operative visit with the OAL provider.

The enrollment phase is projected to take approximately 24 months.

4.1 Total Number of Subjects and Sites

The study enrollment is planned to be 400 subjects who meet eligibility criteria and consent to the study. The study will be conducted at only one (1) site, Lancaster General Hospital.

4.2 Inclusion Criteria

A patient who meets all of the inclusion criteria and none of the exclusion criteria is eligible to participate in this study. Patients are enrolled in this investigation only when they or their legally authorized representative have signed and dated a written Patient Informed Consent.

Inclusion criteria that must be met are the following:

1. Provision of written informed consent
2. Age $\geq$ 65 years
3. Hip fracture location within the femoral neck, intertrochanteric, and subtrochanteric regions
4. Indication for one of the following surgical interventions: hemiarthroplasty, total hip replacement, sliding plate and screw fixation, or intramedullary fixation

4.3 Exclusion Criteria

Patients will be excluded for the following:

1. Indication for closed reduction or percutaneous screw
2. Allergy to TXA
3. Cerebrovascular accident/stroke, active coronary disease/myocardial infarction, or deep vein thrombosis/pulmonary emboli within one (1) month of the fracture
4. Presence of hypercoagulable disorder, including cancer (active disease), elevated blood homocysteine levels, antiphospholipid antibody syndrome and inherited protein deficiencies (antithrombin III, factor V Leiden, protein S & C deficiencies, prothrombin gene mutation)

4.4 Subject Recruitment

Given approximately 75% of the hip fractures in Lancaster County present at Lancaster General Hospital and are operated on by OAL physicians, there is not a need for marketing or advertising to recruit study subjects. OAL's volume of hip surgeries performed in calendar year 2018 was over 300.

Eligible patients based on the above inclusion criteria and not eliminated by the exclusion criteria will be considered potential candidates for the study. Potential subjects will be approached to participate in the TAHFT study in the emergency room department or operating room holding area of LGH prior to hip surgery.

Once enrolled, a subject is expected to comply with the standard follow-up visit schedule.

4.5 Vulnerable Populations

Children, pregnant women, fetuses, neonates, and prisoners are not included in this research study.

The study may include subjects who are not medically or cognitively able to provide consent and authorization for themselves, and people for whom Spanish, Vietnamese, Nepali, or Arabic is their native language. The consent and authorization process for these subjects in addressed in Section 11.2.

5 Study Intervention

The study drug, TXA, is an anti-fibrinolytic. By reducing the conversion of plasminogen to plasmin, it preserves the structure of fibrin and prevents its degradation.

5.1 Intervention Regimen

In joint replacement surgery, TXA is used at a dosage of 1 g in a 100 cc bag of normal saline, administered intravenously within 30 minutes before incision.

5.2 Regulatory Status of the intervention

Intravenous TXA is approved for marketing by the U.S. Food and Drug Administration and is indicated in patients with hemophilia undergoing tooth extraction to reduce blood loss and prevent hemorrhage. Pre-operative administration in joint replacement is an off-label clinical use. The use in the TAHFT study will be an off-label research use for which we are requesting the IRB to make a determination on IND exemption. The research is not intended to be reported to the FDA in support of a new indication or a significant change in labeling or advertising of the drug, and it does not involve a route of administration, dosage level, or population that significantly increases the risks associated with TXA.

5.3 Risks

The literature does not demonstrate significant complications with TXA administered intravenously in the surgical orthopedic total joint population. However, these studies have not analyzed this drug

administered to the high risk population, which includes those with recent ischemic cardiac events (myocardial infarctions) or thromboembolic events (cerebrovascular accident and deep vein thrombosis/pulmonary emboli), and patients with hypercoagulable disorders. Because of the uncertainty whether this drug increases the risk of embolic events, we aim to eliminate patients with ischemic cardiac and thromboembolic events within 30 days prior to surgery, and those with hypercoagulable disorders, which are the highest risk patients. However, we plan to include patients with events that occurred more than 30 days prior to surgery with the aim to learn more about these at-risk patients, in accordance with the recommendations of the American Academy of Orthopedic Surgery and the American Association of Hip and Knee Surgeons as previously cited.

As a precaution, a post-operative dose of TXA will not be given to any subject enrolled in this study.

5.4 Potential Benefits

Administration of TXA may decrease the need for post-operative blood transfusions and the complications associated with transfusions and anemia. TXA may also decrease the rate of readmissions especially related to anemia. There are several studies in the literature that support that TXA administration may be beneficial in decreasing post-operative blood loss in major orthopedic surgery.[14-28] In addition, there are smaller studies examining the hip fracture population showing potential benefit.[5, 29-31]

5.5 Randomization

Based on the kind of fracture, the treating surgeon will decide on the type of surgical procedure to be performed. The surgeon will designate the type of procedure in the order placed in Epic for TAHFT study drug.

Upon receipt of the Epic order, a study trained OR pharmacist will log into the REDCap TAFHT database. The pharmacist enters the consented subject's name, MRN, and the designated surgical procedure (stratum). REDCap generates the subject's Study ID and then the stratified randomization assignment to TXA or placebo.

For subjects randomized to the intervention arm, a pharmacy technician prepares a plain 100 cc normal saline bag with 10 cc of 100mg/cc TXA-saline (110 cc total). For subjects randomized to placebo, a plain 100 cc normal saline bag containing an additional 10 cc of saline (110 cc total) will be used. A TAHFT study label with subject MRN will be affixed to the plain 100 cc normal saline bag. A trained study pharmacist confirms the work of the pharmacy technician and confirms the REDCap randomization assignment and appropriate study drug/placebo saline bag preparation. The saline solution and tranexamic acid will be used from the pharmacy available stock.

Upon approval, the pharmacist technician prepares the study treatment to be picked up by anesthesia in the OR pharmacy location. Anesthesia confirms study subject identity, and blinded study drug is administered prior to surgical incision.

5.6 Blinding

Only the trained study pharmacists will not be blinded to treatment assignment. The operating room staff, surgeon, anesthesiology, research coordinator, and research assistant will be blinded for the duration of the study, as will the subjects themselves.

6 Study Procedures and Data Collection

The schedule of data collection is detailed in the table below.

Table 1: Schedule of Study Procedures and Data Collection

	Enrollment	Surgical Period	Hospital Discharge	2 Week FU	6 Week FU	3 Month FU
Days	-1-0d	0	2-4d	14d ± 7d	45d ± 7d	90d ± 14d
Study Procedures						
Inclusion/Exclusion Criteria Check	X					
Informed Consent/ Assent Procedure	X					
Randomization		X				
Study Drug Administration		X				
Data Collection						
Concomitant Medications		X	X	X	X	X
Laboratory Tests (PT/INR, CBC, CMP, H/H)		X	if done	if done	if done	if done
Transfusions Received		X	X			
Post-surgical Subject Assessment			X	X	X	X
Hospital Readmission					X	X
Adverse Event / Unanticipated Problem / Death Assessment		X	X		X	X

6.1 Enrollment

Hip fracture patients will be evaluated for appropriateness of surgery and follow the standardized pre-operative testing protocol, which will include lab tests to evaluate patient safety including complete blood counts, comprehensive metabolic panels, and prothrombin time. More advanced lab testing and medical imaging, i.e. EKGs, troponins, CT scans, MRIs, ECHOs, etc., will be done at the discretion of the treating surgical and medical teams as indicated.

OAL physicians will evaluate X-rays to classify the fracture and determine the surgical procedure.

Study enrollment procedures involve checking inclusion and exclusion criteria and consenting eligible subjects or their legally authorized representatives. For eligible patients, OAL physicians will follow the Informed Consent process described in Section 11.2 to discuss the study purpose, risks, benefits, and alternatives to participation and to address the questions and concerns of patients or legally authorized representatives. After the consent process is complete, the OAL physician will document the consent process within the Epic subject medical record.

The study physicians will track all hip fracture patients who they screened but did not meet eligibility criteria or who refused study participation. Additionally, the Clinical Research Coordinator (CRC) will obtain hospital data on all hip fracture patients from the fracture liaison service. This information,

which will be recorded in a de-identified manner, will allow assessment of the generalizability of study results.

6.2 Surgical Period

The surgical period includes subject randomization and administration of study drug just prior to surgery. The research subject receives appropriate hip fracture surgical intervention based on their fracture pattern and determination by the treating surgeon.

The CRC will review Epic for peri-operative study data including:
- Lab work: CBC (Complete Blood Count), CMP (Comprehensive Metabolic Panel), PT/INR (prothrombin time and International Normalized Ratio)
- Blood transfusions administered peri-operatively
- Hemoglobin/hematocrit (H/H) levels before and after blood transfusions
- Adverse events

6.3 Follow Up

6.3.1 Hospital Discharge

The CRC reviews Epic for post-operative study data including:
- Lab work: CBC (Complete Blood Count), CMP (Comprehensive Metabolic Panel), PT/INR (prothrombin time and International normalized ratio)
- Blood transfusions administered post-operatively
- Hemoglobin/hematocrit (H/H) levels before and after post-operative blood transfusions
- Adverse events

6.3.2 Follow Up Visits

The subject receives routine hip fracture post-operative care per the LGH geriatric fracture program. The post-hospital observational phase will include a minimum of two post-operative follow-up evaluations at two (2) weeks, six (6) weeks, and three (3) months.

The two (2) week, six (6) week, and three (3) month standard of care post hip surgery patient assessment will include evaluation of the following:
- X-rays to evaluate hip fracture and hardware placement
- Dressing check (2 week only)
- Physical therapy progress
- Weight bearing status
- Pain medication management
- Post-operative anti-coagulation management
- Bone density osteoporosis prevention conversation

The CRC conducts a medical chart review at the 6 week and 3 month time points for scheduled and unscheduled office visits a subject has with any provider for the following items:
- Subject assessment by the OAL provider
- Medication changes and updates
- Laboratory tests (if done)
- Hospital readmission and associated diagnosis in the interim since discharge after hip surgery
- Adverse events

If a subject reports visits or hospitalizations outside the LG system, study personnel will request permission to obtain data from the providers or health systems. If a subject is reported to be deceased during the follow-up period, the CRC will record this event in the study database.

6.4 Unscheduled Visits

It is anticipated that <5% of subjects require an additional unscheduled visit. Typically additional visits are to evaluate wound healing. Any relevant information from these visits will be captured by the medical chart reviews at 6 weeks and 3 month.

7 Statistical Plan

Statistical support will be provided by the Lancaster General Research Institute.

7.1 Sample Size and Power Determination

Power calculations are based on the assumptions that 20% of the control group will require transfusion as a result of the hip fracture and surgery, and that use of TXA will reduce that percentage by half to 10%. For 80% power with a two-sided alpha of 0.05, and using a likelihood ratio test, the sample size is calculated to be 200 per group with a 1:1 assignment ratio, or 400 total subjects.

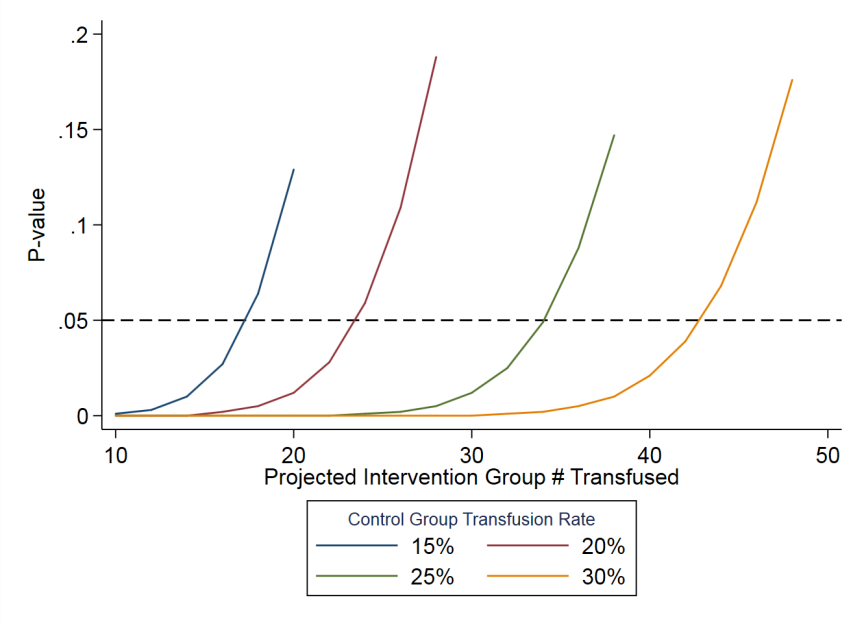
7.2 Statistical Methods

For assessing the primary endpoint, we will calculate an odds ratio (with a 95% confidence interval) for transfusion with p-values calculated using a likelihood ratio.

As a secondary outcome, daily hemoglobin and hematocrit levels will be assessed using a mixed-effects linear model with adjustment for appropriate covariates. Safety/complication outcomes such as 30-day readmissions, embolic events or other complications will be assessed using appropriate binary or Poisson models. Descriptive statistics using appropriate comparative models will be used to assess homogeneity of demographics and any differences in outcomes between the control and intervention groups.

One interim analysis is planned to assess the primary endpoint for significant efficacy sufficient to stop the trial early. The interim analysis is planned for the ¾ point of the trial or a minimum of 300 subjects enrolled. To compensate for one interim and one final analysis, we will employ the O'Brien-Fleming adjustments to significance level criteria with $p < 0.0054$ for the interim analysis and $p < 0.0492$ for the final analysis. Based upon a simulation of our primary outcome, futility will be reached at the interim analysis point if the control group has a 30 (30/150 = 20%) or fewer subjects that have experienced a transfusion and the intervention group has 26 (26/150 = 17.3%) or more subjects that have experienced a transfusion. Even if the remaining 50 intervention subjects to be enrolled experience no transfusions and the transfusion rate remains at 20% in the control group, H_0 will not be rejected.

Futility Boundary Based Upon Control Group Transfusion Rate and Projected Intervention Group Number Transfused



8 Safety and Event Reporting

The study will comply with requirements of the Lancaster General Human Research Protection Program (HRPP) policies regarding reporting of unanticipated problems and adverse events.

8.1 Recording of Adverse Events

Numerous complications or sequelae of hip fracture surgery are outcomes for the study. Only adverse events that are related to the study treatment itself will be considered study adverse events.

At each contact with the subject, clinical personnel will seek information on adverse events by specific questioning and, as appropriate, by examination. This information will be recorded in the electronic medical record. The research coordinator will review and abstract this information into the study database, which will provide systematic recording and classification of a specific list of potential adverse events.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome.

8.2 Relationship of AE to Study

The PI will determine, in his judgment, the relationship of each adverse event to the study procedures should be characterized. The relationship will be classified as probably related, possibly related, or unlikely to be related.

8.3 Reporting of Adverse Events and Unanticipated Problems

Unanticipated problems, as defined by HRPP policy, will be reported to the IRB in accordance with the same policy. All other adverse events, withdrawals, and study deviations will be reported in summary form during the continuing IRB review of the study or in the final report.

9 Data Management and Record Keeping

9.1 Database and Data Management

The study database will be designed and maintained in REDCap, a HIPAA compliant database (Harris et al). Study staff will be granted access to database sections based upon role. Only the pharmacists responsible for randomization will have access to the un-blinded study group assignment assigned by and recorded within REDCap. Research staff will have access to enter data but not extract summary data. Clinical personnel will not have any access to the study database to maintain equipoise and independence. Subject identifiers will be maintained in the database to facilitate the conduct of the study and insure accurate data collection. Upon completion of the study, the database will be locked and subject identifiers will be secured and not connected with the study data. Study data will be maintained in REDCap after completion of the study in archive mode.

The study screening log of patients who are not enrolled in the study will also be maintained in REDCap. The log will not contain any personal identifiers for these patients.

9.2 Records Retention

Study records will be retained for a minimum of 6 years, in accordance with HRPP policy.

10 Study Monitoring

10.1 Quality Assurance Monitoring

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. However, as an investigator-initiated study without an external monitor that conducts monitoring, the TAHFT study will be prioritized for monitoring by the Research Quality Assurance Office of the LG HRPP. Compliance with HRPP policies will be assessed, consent forms will be reviewed, and IRB correspondence and any other regulatory documentation will be checked. Study data may be sampled to be checked for accuracy.

Should any concerns about non-compliance emerge, HRPP policy for review and investigation will be followed.

10.2 Data and Safety Monitoring

The Data and Safety Monitoring Committee (DSMC) for TAHFT comprises four individuals who work at LGH. Because the drug is an approved drug and there is significant experience with its use, it is believed that an internal committee can adequately monitor the trial. The committee will include a trauma surgeon, anesthesiologist, orthopedic surgeon, and orthopedic nurse, as well as a biostatistician. In addition, the principal investigator, Gregory Tocks, DO, will attend committee meetings to address protocol. As the principal investigator, he is the person most familiar with the drug protocol and in the best position to address questions about it. However, he will not participate in any votes about study continuation or termination.

The first meeting of the committee will take place once the 50 subjects have been enrolled or after 6 months, whichever occurs first. Thereafter, the committee will meet biannually to review accumulated safety data and as hoc as needed to review or address any adverse events. The principal investigator will be aware of all adverse events that may occur in the study and will be responsible to call ad hoc meetings of the DSMC if necessary. Specific safety outcomes to be monitored include:

- Rate of 30 day readmissions and reason
- Complications within 90 days from surgery
- Other unanticipated events

One interim analysis will be conducted when 75% of enrollment is achieved to determine if the study should stop early for efficacy or futility. It also will allow assessment of the benefits concordantly with the risks.

11 Ethical Considerations

The study will not begin until it has received approval from the LGH Institutional Review Board (IRB). Any changes to the protocol or consent form that represent potential changes to the risk-benefit ratio or an increase in what is required of subjects will be submitted to the IRB as an amendment for review before it is implemented (unless a delay in implementation would compromise subject safety).

11.1 Risk-Benefit Assessment

The study aims to provide data on the risks and benefits of TXA administration in the geriatric hip fracture population. While other studies have demonstrated benefit without significant complications when given in the orthopedic total joint population, there is not data from large studies conducted in the geriatric hip fracture population. The risks may be greater in this generally higher risk population, but the potential benefit also may be greater if the frequency of blood transfusion is greater. We therefore think the potential risk-benefit ratio is acceptable. The accuracy of this assumption will be assessed as the study is ongoing through safety monitoring and the interim analysis.

11.2 Process for Obtaining Informed Consent and HIPAA Authorization

All subjects will be provided a combined, written consent and HIPAA authorization form that describes the study in sufficient detail for subjects to make an informed decision about their participation in this study. This consent and authorization form will be submitted with the protocol for review and approval by the IRB. The formal consent and authorization of a subject, using the IRB-approved form, will be obtained before that subject undergoes any study procedure.

When obtaining consent and authorization, OAL physicians will discuss the study purpose, risks, benefits, and alternatives to participation and address questions and concerns with patients and their legally authorized representatives, when applicable. Research staff will be involved in the process of obtaining consent and authorization, by discussing with potential subjects the details of the study follow-up, how information about them will be used and disclosed, and who to contact in the case of injury or with questions or concerns. Given that the study is being conducted in the emergency hip fracture population, subjects or their representatives will not have extended time to review the written consent and authorization. Therefore, the physicians and research staff will take special care to ensure that subjects demonstrate understanding of the study in conversation. Subjects or their legally authorized representatives will be asked to sign the written consent and authorization form and will be given a copy of the form. After the consent and authorization process is complete, the OAL physician will document the process within the Epic subject medical record.

The OAL physician will make the determination as to whether a subject is medically or cognitively unable to give consent and authorization and who is appropriate to serve as the subject's legally authorized representative, following LG policies. The subject will be informed about the trial to the extent compatible with the subject's capacity for understanding. If the legally authorized representative is not available in person, the consenting physician may transmit the consent form to the representative electronically and discuss the study with the representative by phone. The legally authorized representative may return a signed copy by fax or email or in person prior to randomization. Alternatively, electronic signature may be obtained via the study database in REDCap.

For uses of a short form, an alteration of the HIPAA authorization requirement is requested. That is, in these circumstances, authorization to use and disclose health information will be obtained orally, but no signature will be obtained in the HIPAA authorization section of the consent form.

11.3 Withdrawal of Consent or Revocation of Authorization

Participation in TAHFT study is voluntary. Research subjects may withdraw, or their legally authorized representatives may withdraw them, from the study at any time during the course of the study. Refusing to participate or withdrawing from the research study will not impact a patient's medical care.

Unless a subject withdraws soon after consent and before surgery, it is likely that the study intervention will be completed. That is, when a subject withdraws from the study after surgery, s/he is withdrawing only from follow-up data collection from the medical record.

Some subjects or legally authorized representatives may wish to withdraw medical care. An OAL physician will review with them the standardized routine hip fracture follow up care for 90 days after surgery. If the subject or legally authorized representative desires to completely withdraw medical care, the OAL provider will document and monitor outcomes via phone calls or chart reviews. Also, if a subject relocates out of the Lancaster, PA, geographical area during the acute post-operative period, OAL will monitor subject outcomes via phone calls. Subjects will be asked if this information may be used in the research study.

Study data collection stops upon subject withdrawal from TAHFT study. For example, if subjects withdraw from the TAHFT study prior to surgery, operative and post-operative data will not be collected. Data that have already been collected up until study withdrawal will remain part of the TAHFT study database.

11.4 Privacy and Confidentiality

Patients will be approached about participating in the study in the emergency room, patient hospital room, or the pre-operative room. They will be extended as much privacy as possible, with conversations about the study occurring in the context of therapeutic decision-making. All follow-up interactions with participants also will occur in the context of medical care.

The use of subjects' medical data for research purposes will be explained in the consent and authorization process. The study database will contain the participants' names and medical record numbers to facilitate the conduct of the study. The study database will be accessible only to study personnel, as described in Section 9.1.

Identifiable data will not be disclosed outside of LG Health. However, subjects will be informed that their study data could be de-identified and shared with other researchers.

Data on hip fracture patients who do not participate in the TAHFT study will be recorded in a de-identified manner, to allow assessment of the generalizability of the patient population and study results.

12 Study Finances

12.1 Funding Source

Funding for this study will be financed through a grant from the von Hess Foundation.

12.2 Conflict of Interest

Research investigators and personnel are required to disclose any financial interests related to their job responsibilities on an annual basis. Financial interests are reviewed by the Research Compliance Committee as protocols are submitted and as they come up for continuing review. Any potential conflicts of interest must be managed to the satisfaction of the IRB to minimize influence on subject safety and study integrity.

12.3 Subject Stipends or Payments

The study participant will not incur additional costs from participating in this study. There are no programs to pay for medical care necessitated by adverse events associated with participation in this study. Payment for care for adverse events associated with TXA drug administration will be the responsibility of the subject or the subject's third party payer. Subjects will not receive any remuneration for participation.

13 Publication Plan

After completion of the study and analysis of the data, a manuscript for publication will be written with the principal investigator as the lead author. The manuscript will be targeted for publication in an orthopedic journal.

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