



**YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE**

**Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)**

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project:

Safety and Efficacy of Oral Tranexamic Acid in Reducing Blood Loss and Transfusion in Femoral Neck, and Intertrochanteric Femur Fractures

Principal Investigator:

Michael P. Leslie, DO

Yale Academic Appointment:

Assistant Professor

Department: Orthopaedics and Rehabilitation

Campus Address:

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Protocol Correspondent Name & Address (if different than PI):

Adrian Wyllie, MD and Stephen Nelson, MD

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Yale Cancer Center CTO Protocol Correspondent Name & Address (if applicable):

N/A

Campus Phone:	Fax:	E-mail:
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Business Manager:

Campus Phone :	Fax :	E-mail
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Faculty Advisor: (required if PI is a student, resident, fellow or other trainee)	<input checked="" type="checkbox"/> NA	Yale Academic Appointment:
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Campus Address:

Campus Phone:	Fax:	Pager:	E-mail:
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Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
<http://www.yale.edu/hrpp/policies/index.html#COI>

Yes No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

Yes No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: <http://www.yale.edu/coi/>

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. Performing Organizations: Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- | | |
|--------------------------------------------------------------------------|------------------------------------------------------------------|
| <input type="checkbox"/> Magnetic Resonance Research Center
(MR-TAC) | <input type="checkbox"/> Yale University PET Center |
| <input type="checkbox"/> Yale Cancer Center/Clinical Trials Office (CTO) | <input type="checkbox"/> YCCI/Church Street Research Unit (CSRU) |
| <input type="checkbox"/> Yale Cancer Center/Smilow | <input type="checkbox"/> YCCI/Hospital Research Unit (HRU) |
| | <input type="checkbox"/> YCCI/Keck Laboratories |

- Yale-New Haven Hospital
 Cancer Data Repository/Tumor Registry
 Specify Other Yale Location:

Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

- | | |
|------------------------------------------------------------------------------|----------------------------------------------------------------|
| <input type="checkbox"/> APT Foundation, Inc. | <input type="checkbox"/> Haskins Laboratories |
| <input type="checkbox"/> Connecticut Mental Health Center | <input type="checkbox"/> John B. Pierce Laboratory, Inc. |
| <input type="checkbox"/> Clinical Neuroscience Research Unit (CNRU) | <input type="checkbox"/> Veterans Affairs Hospital, West Haven |
| <input type="checkbox"/> Other Locations, Specify:
(Specify location(s)): | <input type="checkbox"/> International Research Site |

c. Additional Required Documents (check all that apply):

- | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <input type="checkbox"/> *YCCI-Scientific and Safety Committee (YCCI-SSC) | X N/A |
| <input type="checkbox"/> *Pediatric Protocol Review Committee (PPRC) | Approval Date: |
| <input type="checkbox"/> *YCC Protocol Review Committee (YRC-PRC) | Approval Date: |
| <input type="checkbox"/> *Dept. of Veterans Affairs, West Haven VA HSS | Approval Date: |
| <input type="checkbox"/> *Radioactive Drug Research Committee (RDRC) | Approval Date: |
| <input type="checkbox"/> YNHH-Radiation Safety Committee (YNHH-RSC) | Approval Date: |
| <input type="checkbox"/> Yale University RSC (YU-RSC) | Approval Date: |
| <input type="checkbox"/> Magnetic Resonance Research Center PRC (MRRC-PRC) | Approval Date: |
| <input type="checkbox"/> *Nursing Research Committee | Approval Date: |
| <input type="checkbox"/> YSM/YNHH Cancer Data Repository (CaDR) | Approval Date: |
| <input type="checkbox"/> Dept. of Lab Medicine request for services or specimens form | |
| <input type="checkbox"/> Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at
http://radiology.yale.edu/research/ClinTrials.aspx | |

**Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.*

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

-1 year

3. **Research Type/Phase: (Check all that apply)**

a. **Study Type**

- Single Center Study
 Multi-Center Study

Does the Yale PI serve as the PI of the multi-site study? Yes No

- Coordinating Center/Data Management
 Other:

b. **Study Phase** X N/A

Pilot Phase I Phase II Phase III Phase IV
 Other (Specify)

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

X Clinical Research: Patient-Oriented Clinical Research: Outcomes and Health Services
 Clinical Research: Epidemiologic and Behavioral Interdisciplinary Research
 Translational Research #1 ("Bench-to-Bedside") Community-Based Research
 Translational Research #2 ("Bedside-to-Community")

5. Is this study a clinical trial? Yes X No

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov X
 Other (Specify)

Registration of clinical trials at their initiation is required by the FDA, NIH and by the ICMJE.

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, <http://ycci.yale.edu/researchers/ors/registerstudy.aspx> or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
 Yes X No

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance*

(Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

Yes No

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes No *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **NO**

c. Will a novel approach using existing equipment be applied? **NO**

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply.

Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Michael P. Leslie, DO			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input checked="" type="checkbox"/> Other, Specify: Dept of Orthopedic Surgery
			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
 Company:
 Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	Affiliation: Yale/Other Institution (Identify)	NetID

Principal Investigator	Michael P. Leslie, DO	YNHH	mpl6
Role: Resident Researcher	Adrian Wyllie, MD	YNHH	aw664
Role: Resident Researcher	Daniel Wiznia, MD	YNHH	Dhw23
Role: Resident Researcher	Stephen Nelson, MD	YNHH	sn364
Role: Resident Researcher	Havalee Henry, MD	YNHH	Hth3
Role:			
Role:			

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the [University](#) and qualify to serve as the

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

Yes (provide a description of that interest in a separate letter addressed to the HIC.)

No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

Yes (provide a description of that interest in a separate letter addressed to the HIC)

No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

Chair Name (PRINT) and Signature

Date

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

YNHH HSPA Name (PRINT) and Signature

Date

SECTION V: RESEARCH PLAN**1. Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The primary objective of this study is to assess the safety and efficacy of Tranexamic acid (TXA) in reducing blood loss and transfusion requirements for patients with osteoporotic hip fractures. In addition to assessing blood loss in these patients, complications associated with TXA use would be characterized including systemic (pulmonary embolism, deep venous thrombosis, myocardial infarction, stroke) and surgical site (hematoma, infection) events, need for re-hospitalization or re-operation and 30 day mortality.

2. Background: Describe the background information that led to the plan for this project.

Provide references to support the expectation of obtaining useful scientific data.

Hip fractures are associated with significant blood loss and a subsequent need for blood transfusion. The causes of bleeding are multifactorial, increased fibrinolytic activity being one of them.^{1, 2} The use of allogenic blood products is expensive and is associated with increased risk of hemolytic and anaphylactic reactions, post-operative infections¹ and lengthened hospital stay. Tranexamic acid (TXA) is a simple and inexpensive pharmacologic agent that inhibits fibrinolysis and reduced bleeding.^{1, 2} It has a 44 year history of clinical use beginning with patients with symptomatic menorrhagia as well as bleeding prophylaxis in hemophiliac patients undergoing tooth extraction

TXA is an antifibrinolytic medication (reduces the destruction of blood clots, thus promoting the ability to stop bleeding) that is frequently used to reduce perioperative blood loss, blood transfusions and associated costs in major cardiac, vascular, obstetric, and orthopedic procedures. It has been used successfully in orthopedics to reduce perioperative blood loss, particularly in spine surgery^{5, 6, 7} total knee and total hip arthroplasty (THA)^{9,10}. Multiple recent meta-analyses have found that use of TXA in the setting of total knee arthroplasty (TKA) and THA leads to significantly less overall blood loss and lower rates of blood transfusion without increasing rates of venous thromboembolism (VTE) or other complications^{11,12}.

Osteoporotic hip fractures are at an increased risk for acute blood loss than elective orthopaedic surgery patients because they are exposed to a double bleeding insult. Fractures bleed and many of these patients sustain their first hit when hematoma forms in their soft

tissues leading to symptomatic anemia. Subsequently these patients sustain additional blood loss when they undergo surgery for definitive treatment of their injuries.

Trauma surgeons understand the risk of hemorrhage associated with trauma and routinely give TXA to patients who present with high energy injuries. The CRASH-2 trial was an international study which randomized 20,000 bleeding trauma patients to get IV TXA or matching placebo upon presentation. With 99.5% follow up, the authors noted a decreased risk of bleeding and death without ill effect.¹³

Although several previous studies have used IV TXA to reduce blood loss, TXA has proved to be an effective antifibrinolytic agent in IV, topical and oral formulations. Oral preparations of the drug may be preferred due to their equivalent efficacy and lower cost.¹⁴

There are limited data the use of TXA in patients with hip fractures. We propose a double-blinded, randomized, controlled trial comparing perioperative administration of TXA to placebo in the setting of hip fractures. Thus our goal is to examine the safety and efficacy of TXA in reducing blood loss and red blood cell requirement for patients with hip fractures at the time of hospital admission.

Informed consent will be obtained from the patient or health care proxy upon diagnosis of hip fracture by the orthopedic consult resident or research coordinator. At that time, study subjects will be randomized to two groups. The two patient groups will include:

1. 1.95g of oral tranexamic acid upon presentation to the emergency department and again 2 hours prior to surgery.
2. Placebo tablets in the emergency department and again 2 hours prior to surgery.

Pharmacy will keep the surgeon blinded to the treatment group that the patient is randomized into. Blood loss following surgery will be evaluated during the entire in-patient stay of the study subjects. Patients will also be surveyed about related complications and/or re-hospitalizations at their first postoperative office visit (2-3 weeks post-operative).

1. Mannucci PM, Levi M. Prevention and treatment of major blood loss. *N Engl J Med* 2007; 356: 2301–11
2. Sculco TP. Global blood management in orthopaedic surgery. *Clin Orthop Relat Res* 1998;357:43-9
3. Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion* 1999;39: 694–700
4. Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. *Lancet* 2007;370: 415–26
5. Cherian T, Maier S P II, Bianco K, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. *Spine J.* 2015;15(4):752–761.
6. Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS ONE.* 2013; 8(2):e55436.

7. Li Z-J, Fu X, Xing D, Zhang H-F, Zang J-C, Ma X-L. Is tranexamic acid effective and safe in spinal surgery? A meta-analysis of randomized controlled trials. *Eur Spine J.* 2013;22(9):1950–1957.
8. Zhang F, Wang K, Li F-N, et al. Effectiveness of tranexamic acid in reducing blood loss in spinal surgery: a meta-analysis. *BMC Musculoskeletal Disord.* 2014; 15:448
9. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014; 349:g4829.
10. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am* 2012; 94:1153–9
11. Veien M, Sørensen JV, Madsen F, Juelsgaard P. Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. *Acta Anaesthesiol Scand.* 2002 Nov;46 (10):120611.
12. Kakar PN, Gupta N, Govil P, Shah V. Efficacy and Safety of Tranexamic Acid in Control of Bleeding Following TKR: A Randomized Clinical Trial. *Indian J Anaesth.* 2009 Dec;53(6):66771
13. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, Cook L, Kawahara T, Perel P, Prieto-Merino D, Ramos M, Cairns J, Guerriero C. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess.* 2013 Mar;17(10):1-79. doi: 10.3310/hta17100.
14. Fillingham YA, Kayupov E, Plummer DR, Moric M, wyGerlinger TL, Della Valle CJ. The James A. Rand Young Investigator's Award: A Randomized Controlled Trial of Oral and Intravenous Tranexamic Acid in Total Knee Arthroplasty: The Same Efficacy at Lower Cost? *J Arthroplasty.* 2016 Sep;31(9 Suppl):26-30. doi: 0.1016/j.arth.2016.02.081. Epub 2016 Mar 19.
15. McIntyre CW, Owen PJ. Prescribing drugs in kidney disease. In: Brenner BM, edr. *Brenner & Rector's The Kidney.* Philadelphia: Saunders, an imprint of Elsevier Inc.; 2008. p. 1930-53.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths.** Describe the setting in which the research will take place.

The study will be a blinded prospective randomized controlled trial, looking at the effect of Tranexamic Acid on perioperative blood loss and transfusion rates in patients presenting with femoral neck or intertrochanteric femur fractures. Study subjects will be randomized to receive either oral TXA (1.95g) or placebo tablet. One dose will be given by upon presentation to the ED and a second dose will be given 2 hours prior to surgery.

Currently use for tranexamic acid became available on both campuses (SRC and YSC) as of 6/1/13 for prevention of bleeding in orthopedic joint procedures (total knees and total hips) as approved at the May 2013 Pharmacy & Therapeutics (P&T) Committee Meeting.

Both patients and the treating surgeons will be blinded with regard to placebo vs. treatment until completion of the study. All patients will be treated surgically according to the definitive fixation required by each specific fracture pattern. These potential surgical interventions include total hip arthroplasty, hemiarthroplasty, intramedullary fixation, blade plates, or sliding hip screws in accordance with standard of care.

Meticulous hemostasis will be done as per standard of care in any operative case.

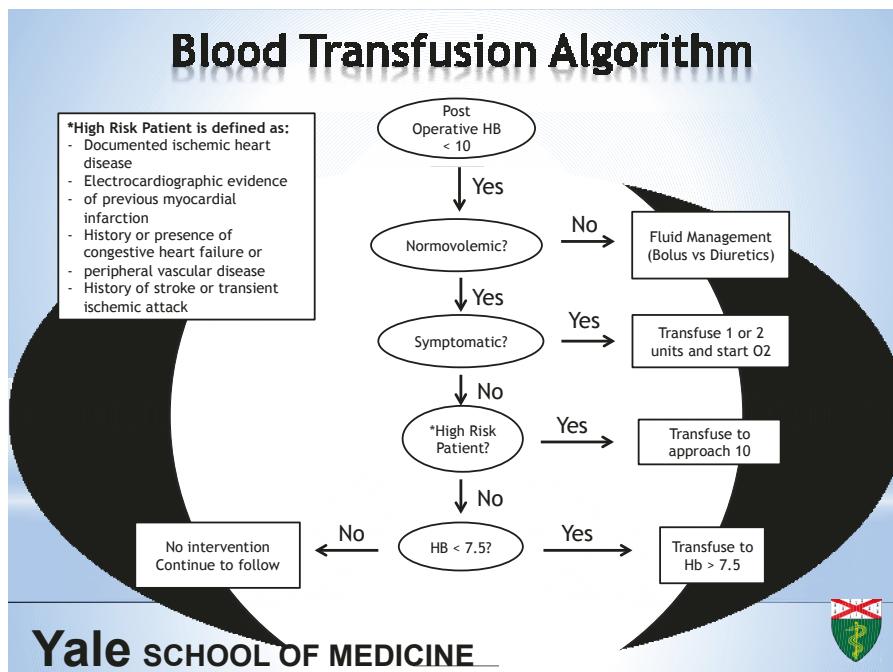
Blood loss will be assessed using the Lisander formula¹ where Estimated blood loss = (Blood Volume * Hctⁱ * 0.01) + Vt + Va – (Blood Volume * Hct^e * 0.01) where Blood Volume is calculated using Nadler's formula; Hctⁱ is the preoperative haematocrit, Hct^e is the haematocrit at the end of the hospital stay, Vt is the volume of allogeneic RBC transfused and Va is the volume of RBC returned by the autotransfusion device. Volumes are all in millilitres.

Blood volume is calculated using the Nadler equation (0.006012 x Height³)+(14.6 x Weight)+604.

transfusions will be made according to the standard blood transfusion algorithm below.

Additional data being collected include hospital length of stay, patient demographics including ASA class. Complications will be recorded as they occur or at 2 and 6 week follow up. Both of these visits will be in-person at their scheduled follow up clinic appointments.

1. Lisander B, Ivarsson I, Jacobsson SA (1998) Intraoperative autotransfusion is associated with modest reduction of allogeneic transfusion in prosthetic hip surgery. *Acta Anaesthesiol Scand* 42:707–712



Genetic Testing N/A X

A. Describe

- the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
 - the plan for the collection of material or the conditions under which material will be received
 - the types of information about the donor/individual contributors that will be entered into a database
 - the methods to uphold confidentiality
- B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
- C. Is widespread sharing of materials planned?
- D. When and under what conditions will materials be stripped of all identifiers?
- E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
- How will requests to withdraw materials are handled (e.g., material no longer identified: that is, anonymized) or material destroyed?
- F. Describe the provisions for protection of participant privacy
- G. Describe the methods for the security of storage and sharing of materials

4. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

- Adults 18 years and older. There is no upper age limit.
- Femoral neck and intertrochanteric femur fractures who present to the emergency department after a low energy mechanism. Low energy injuries result in fractures in patients whose bone integrity is compromised after a mechanism which would not have otherwise fractured healthy bone. An example is a fall from standing in a patient with osteoporotic bone.
- Osteoporotic hip fractures

5. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

- | | | |
|------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------------|
| <input type="checkbox"/> Children | <input checked="" type="checkbox"/> Healthy | <input type="checkbox"/> Fetal material, placenta, or dead fetus |
| <input type="checkbox"/> Non-English Speaking | <input type="checkbox"/> Prisoners | <input type="checkbox"/> Economically disadvantaged persons |
| <input type="checkbox"/> Decisionally Impaired | <input type="checkbox"/> Employees | <input type="checkbox"/> Pregnant women and/or fetuses |
| <input type="checkbox"/> Yale Students | <input type="checkbox"/> Females of childbearing potential | |

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? Yes No (If yes, see Instructions section VII #4 for further requirements)

6. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Adult subjects 18 years of age or older will participate in this study after the objectives, methods, and potential hazards of the study have been fully explained, and after they have signed the informed consent form. The Investigator or designee is responsible for keeping a record of all subjects who sign an informed consent form for entry into this study. To be enrolled into the study, subjects must meet the following inclusion/exclusion criteria.

Inclusion Criteria:

- Patients presenting with femoral neck and intertrochanteric femur fractures
- Patients age 18 and older. There is no upper age limit.
- Low energy injury

Exclusion Criteria:

- Pregnant* or breast-feeding women

- Allergy to tranexamic acid
- Acquired disturbances of color vision
- A history of arterial or venous thromboembolism
 - Cerebral Vascular Accident
 - Deep Vein Thrombosis
 - Pulmonary Embolism
- Subarachnoid hemorrhage
- Active intravascular clotting
- Concomitant use of tranexamic acid with Factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid (oral tretinoin) may increase the risk of thrombosis.
- Renal dysfunction (serum creatinine >1.5 or creatinine clearance < 50 ml/min)
- *All women of child bearing potential must have a negative serum or urine pregnancy test.

7. How will **eligibility** be determined, and by whom?

The primary surgeon and the above residents will determine eligibility in the emergency department. The primary diagnosis for surgery will be used to confirm inclusion criteria and then patient history will be conducted to rule out any contraindications to tranexamic acid. Subjects will also be excluded if they declined to participate. Surgical consent will be obtained first and within 30 minutes, research consent will be obtained after discussion of the research trial versus the standard of care.

Surrogate consent will be obtained for subjects unable to provide consent. The consent will be obtained in person if the surrogate is present or via a telephone with the help of a witness. Re-consenting will also be obtained when applicable.

8. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Most frequently reported adverse effects are minor gastrointestinal symptoms such as nausea and vomiting, especially when administered at high dose or injected rapidly. Higher doses of TXA (100 mg/kg or more), much higher than what will be used in this trial (maximum of two doses of 1.95g), have been associated with a higher incidence of seizures in cardiac patients (TXA crosses the blood-brain barrier and it is believed that a TXA-mediated inhibition of glycine receptors may underlie the effect). It is unclear why most episodes of seizures occur during immediate postoperative hours, when levels of intraoperatively administered TXA in the serum and cerebrum should already be declining. One possibility is that TXA induces modifications (neuroplasticity) in these inhibitory circuits that outlast its pharmacological time course. There is higher incidence of TXA-related seizures in patients undergoing open

heart procedures may relate to disruption of BBB integrity by cerebral emboli, which known to be much more prevalent during open-heart procedures versus coronary artery bypass grafting.

- persistent atrial fibrillation
- increased risk of seizures and with renal complications following their use in cardiac surgery.
- may increase risk of disseminated intravascular coagulation (DIC).
- need for caution in the use of these agents in patients with hematological malignancies as they are at increased risk of DIC
-

Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present, prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded as an AE rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from signature of the informed consent form through 6 week post-operative period. AEs will be recorded on the data collection form. All AEs will be followed until resolved. Any AEs uncovered during routine postoperative care visits or review of the EMR will also be reported for study purposes.

Project specific AEs Exempt From Reporting

Certain adverse events would be expected to occur in hip fracture patients regardless of the use of the investigational product TXA. Therefore, within the post-surgical period, the following adverse events will be excluded from collection unless they are of a severity or frequency greater than would be expected for this post-surgical patient population.

- Intraoperative fracture
 - Uncommon
 - Higher risk in revision setting
- Hematoma
 - Low risk with postoperative drains
- Infection
 - Reported risk 1-10%
 - May be higher in rheumatoid
 - Higher in revision setting
- Implant Failure
 - Uncommon
- Medical risks
 - Blood transfusion reaction

- Pneumonia

However, the PI will report the following adverse events that can occur during the post-op period:

- Myocardial infarction
- Stroke
- Deep venous thrombosis
- Pulmonary embolus
- Death

Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Requires treatment, modification/interruption of study medication dose, or any other therapeutic intervention.
- Is judged by the investigator to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome would be recorded. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality would be recorded as the AE.

Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the investigator the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to study medication, action taken regarding study medication, and outcome.

Classification of severity

The severity of adverse events (AEs) will be graded on a scale of 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events ([The NCI Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE]. The NCI CTCAE can be viewed on-line at the following NCI web site:

<http://ctep.cancer.gov/reporting/ctc.html>

If a specific event is not included in the NCI CTCAE toxicity scale, the following scale will be used to grade the event:

<u>Grade</u>	<u>Definition</u>
1	Mild Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2	Moderate Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic maneuvers
3	Severe Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4	Life-threatening Immediate risk of death; requires hospitalization and clinical intervention.
5	Death

Classification of Relationship/Causality of adverse events (AE/SAE) to study drug

The investigator will determine the relationship between the administration of study drug and the occurrence of an AE/SAE as not suspected or suspected as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes a **causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event

Suspected: The temporal relationship of the adverse event to study drug administration makes a **causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Unknown The temporal relationship of the adverse event to study drug administration makes a causal relationship unable to determine or unknown

Monitoring and reporting of adverse events

All subjects will be monitored for AEs between the signing of the informed consent and 6 weeks postop. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical

examination findings; or other appropriate tests and procedures. Any AEs uncovered during routine postoperative care visits will be reported for study purposes.

9. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

The above risks are more pronounced in cardiac surgery patients, not orthopaedic surgery patients. Nonetheless, the patients will be carefully monitored intraoperatively as well as postoperatively. They will be given an antiemetic if necessary and started on proton-pump inhibitor (PPI) if indicated.

Only the listed investigators will have access to the data, and no access will be given to anyone not involved in the collection and analysis of this data. Data will be kept in an excel spreadsheet and stored on encrypted computer without patient names or dates of birth. All data will be destroyed when the manuscript is published

10. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

- a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Above Minimal Risk
- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? No Subjects <18 years old
- c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here <http://www.yale.edu/hrpp/forms-templates/biomedical.html> for
 - i. Minimal risk
 - ii. Greater than minimal

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the

principal investigator, the IRB or Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with the tranexamic acid administration as minimal risks.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Michael P. Leslie, DO according to the following categories:

- a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
- b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
- c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
- d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
- e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;

4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets **ALL 3** of the following criteria:

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

Is related or possibly related to participation in the research (*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); AND

Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. **Please note** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

- All Co-Investigators listed on the protocol.
- Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
- Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator Michael P. Leslie, DO will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

- d. For multi-site studies for which the Yale PI serves as the lead investigator:
 - i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
 - ii. What provisions are in place for management of interim results?
 - iii. What will the multi-site process be for protocol modifications?

11. Statistical Considerations: Describe the statistical analyses that support the study design.

Desai cites a 39.5% rate of transfusion with fixation of hip fractures¹, which is similar to the rate of transfusion we have observed among our own patient population. The use of TXA has been associated with a decreased risk ratio of transfusion of 2.51 for those patients receiving oral TXA for total hip replacement, a similar type of procedure.

Based upon these numbers:

80% power

$\alpha=0.05$

two-tailed test

Likelihood of transfusion: 39.5%

Risk ratio with TXA is 2.51

Predicted sample size is 50.

1. Sagar J. Desai, MD, Kristi S. Wood, MSc, MD, Jackie Marsh, MSc, PhD, Dianne Bryant, MSc, PhD, Hussein Abdo, BSc, Abdel-Rahman Lawendy, MSc, MD, and David W. Sanders, MD, MSc Factors affecting transfusion requirement after hip fracture: Can we reduce the need for blood? *Can J Surg.* 2014 Oct; 57(5): 342–348.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Tranexamic Acid – multiple different approvals, in the IV form as well as topical form for reducing blood loss and transfusion requirement in hip fractures.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

- a. What is the Investigational New Drug (IND) **number** assigned by the FDA? N/A
 - b. Who holds the IND? N/A
 - c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____ N/A _____
- Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate) _____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)

Go to <http://rsc.med.yale.edu/login.asp?url=myApps.asp>. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories*):

Exempt Category 1

The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

- i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. X Yes No
- ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. X Yes No
- iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. X Yes No
- iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). X Yes No
- v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. X Yes No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

- i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
 - Blood grouping serum
 - Reagent red blood cells
 - Anti-human globulin
- ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
- iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

- The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.
2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Tranexamic acid (TXA) is a synthetic antifibrinolytic drug released in the 1970s. Has ten times the potency of Σ -amino-caproic acid (EACA) – the prototypical antifibrinolytic [7].

Mechanism of action - synthetic derivative of the amino acid lysine (competitive blockade of the lysine- binding sites of plasminogen, plasmin, and tissue plasminogen activator). The reversible blockade impedes fibrinolysis and blood-clot degradation. Plasmin inhibition by TXA may also help prevent platelet degradation.

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss. Numerous studies support the premise that TXA reduces blood loss, statistically significant reduction in transfusion (by one – third) rates and reduces the financial cost of surgery. Kogoma 2009 systematic review of randomized trials on MEDLINE, EMBASE, CINAHL and the Cochrane databases reported the efficacy of antifibrinolytic agents in reducing bleeding and transfusion in patients undergoing total hip or total knee replacements who received a prophylactic dose of antifibrinolytic agents.

Very cost effective - Guerriero 2011 reported that administration of TXA within three hours of injury to bleeding trauma patients has been estimated to save 755 life years (LYs) per 1000 trauma patients in the UK, and the incremental cost of giving TXA versus not giving TXA was estimated at USD 48,002 in the UK, equivalent of a cost of around USD 64 per life-year saved.

Tranexamic acid reduces all-cause mortality in bleeding trauma patients, with no apparent increase in the risk of vascular occlusive events. This conclusion is based on the results of the CRASH-2 2010 trial which recruited 20,211 bleeding trauma patients from 274 hospitals in 40 countries.

Dosing

- Wide range depending on the indication.
- Both systemic and topical use of tranexamic acid has been reported to be efficacious.
- Oral
- Topical
- Total Knee Arthroplasty:

Dosage adjustments recommended in patients with renal insufficiency.

Description of previous human use:

Nonsurgical

- management of bleeding associated with leukemia, ocular bleeding, recurrent hemoptysis, menorrhagia, hereditary angioneurotic angio-edema

Surgical

- Orthopaedic surgery (TKA, THA, Spine surgery)
- Cardiac Surgery (cardiopulmonary bypass), pediatric cardiac surgery
- Orthotopic liver transplantation as accelerated fibrinolysis is one of the main causes of excessive bleeding
- Dental surgery

Concerns

- TXA does not increase the risk of thromboembolic complications such as deep-vein thrombosis, pulmonary embolism, thrombotic cerebral vascular accident, or myocardial infarction
- Concerns in hip and knee arthroplasty have been perceived increased risk of thromboembolism in a high-risk predisposed population. However, most recent reports have found no difference in the rates of deep vein thrombosis and pulmonary embolism between patients receiving tranexamic acid and comparison cohorts.
- Recent large Cochrane review of over 25,000 patients (Henry 2011), the use of TXA or EACA was not associated with an increased risk of mortality, myocardial infarction, deep vein thrombosis, stroke, incidence of renal dysfunction
- Common misconception is that these drugs are procoagulants and that they will increase blood clotting. The drugs do not alter blood clotting, but instead slow dissolution of blood clots. Sites where clots have formed will therefore remain or enlarge, but spontaneous formulation of clots should not occur

Known risks/adverse events

- Most frequently reported adverse effects are minor gastrointestinal symptoms such as nausea and vomiting, especially when administered at high dose or injected rapidly.
- Higher doses of TXA (100 mg/kg or more), much higher than what will be used in this trial (less than 30mg/kg), have been associated with a higher incidence of seizures in cardiac patients (TXA crosses the blood–brain barrier and it is believed that a TXA-mediated inhibition of glycine receptors may underlie the effect).
 - o Unclear why most episodes of seizures occur during immediate postoperative hours, when levels of intraoperatively administered TXA in the serum and cerebrum should already be declining.
 - o Possibility is that TXA induces modifications (neuroplasticity) in these inhibitory circuits that outlast its pharmacological time course
 - o Higher incidence of TXA-related seizures in patients undergoing open heart procedures may relate to disruption of BBB integrity by cerebral emboli, which known to be much more prevalent during open-heart procedures versus coronary artery bypass grafting
- Persistent atrial fibrillation
- Increased risk of seizures and with renal complications following their use in cardiac surgery.
- May increase risk of disseminated intravascular coagulation (DIC).
- Need for caution in the use of these agents in patients with hematological malignancies as

they are at increased risk of DIC

Data addressing dosage(s)

- Several systematic reviews have investigated the dosing regimen
- Total dose of TXA used in the trials ranged from 5.5 to 300 mg/kg.
- Median dose was 22 mg/kg, with majority of trials (70 per cent) using total dose of 30mg/kg or less.
- Data suggested effect of TXA on blood loss did not vary over the dose range assessed
- Total dose of 1 g likely to be sufficient for most adults,
- Typical loading dosing for tranexamic acid is 10 mg/kg and this usually followed by continuous infusion of 1 mg/ kg/h for 6 hours.

Interval(s)

- Half life of TXA ~ 80 min, provided there is normal renal function. One dose (oral) will be given on arrival in the ED and a second dose will be given at the time of surgical incision.

Route(s) of administration as described in previous studies:

- Oral
- Topical :
 - o Plasma concentrations following the topical application of TXA are less than one tenth of the level after IV administration
 - o Because there is less systemic absorption, the direct application of TXA to the bleeding surface has potential to reduce bleeding with minimal systemic effects
 - o Clinical scenarios: epistaxis, traumatic hyphemia, gastrointestinal bleeding, surgical bleeding and uterine bleeding
 - o Administered in saline solution (3 grams of TXA) in 100 cc of normal saline) directly on to operative site, either by pouring or spraying into the surgical wound or as a mouthwash in the dental surgery
 - o Gel, Spray, mouth wash
- Intravenous (majority)
- Intra-articular injection (TKA,THA) –
 - o One study looked at solution containing 250-mg (5 ml) or 500-mg (10 ml) of TXA which was added with physiologic saline to create a total volume of 25 ml.
 - o Demonstrated that intra-articular application with low-dosage TXA, as 250 and 500 mg, was effective for reducing postoperative blood loss

References

1. Roberts I, Shakur H, Ker K, and Coats T. Antifibrinolytic drugs for acute traumatic injury.

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9. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 7.
10. Schwinn D.A., Mackensen G.B., Brown E.N. Understanding the TXA seizure connection *J Clin Invest.* 2012; 122(12):4339–4341. doi:10.1172/JCI66724.

3. **Source:** a) Identify the source of the drug or biologic to be used.

- b) Is the drug provided free of charge to subjects? Yes No
If yes, by whom?

The pharmacy department will provide the drug or placebo and then bill The Department of Orthopaedics.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Check applicable Investigational Drug Service utilized:

- YNHH IDS
 CMHC Pharmacy
 PET Center
 Other:

- Yale Cancer Center
 West Haven VA
 None

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

1. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

There are currently no other parental formulas to decrease blood to our knowledge.

- b. State the maximum total length of time a participant may receive placebo while on the study.

1 day

- c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.

No real harmful effects as crystalloid fluids are given in almost all surgical cases.

- c. Describe the procedures that are in place to safeguard participants receiving placebo.

There is nothing to be safeguarded against.

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?

- Yes No *See HIC Application Instructions to view controlled substance listings.*

If yes, is the use of the controlled substance considered:

- Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.

- Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License.*

Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.

7. Continuation of Drug Therapy After Study Closure X Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

- Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.
- No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? Yes No *If Yes, please be aware of the following requirements:*
 - a. A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on “Add new” under the New Technology Request Summary and fill out the forms requested including the “Initial Request Form,” “Clinical Evidence Summary, “ and attach any other pertinent documents. Then select “save and submit” to submit your request;** and
 - d. Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.
2. What is the name of the device to be studied in this protocol? **N/A**

Has this device been FDA approved? Yes No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
4. **Source:**
 - a) Identify the source of the device to be used.
 - b) Is the device provided free of charge to subjects? Yes No
5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

- Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

- Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions, Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf to determine if these pertain to this study.*

- Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability:**

- a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

- a. targeted for enrollment at Yale for this protocol 50
- b. If this is a multi-site study, give the total number of subjects targeted across all sites

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

- | | | |
|----------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------|
| <input type="checkbox"/> Flyers | <input type="checkbox"/> Internet/Web Postings | <input type="checkbox"/> Radio |
| <input type="checkbox"/> Posters | <input type="checkbox"/> Mass E-mail Solicitation | <input type="checkbox"/> Telephone |
| <input type="checkbox"/> Letter | <input checked="" type="checkbox"/> Departmental/Center Website | <input type="checkbox"/> Television |
| <input type="checkbox"/> Medical Record Review | <input type="checkbox"/> Departmental/Center Research Boards | <input type="checkbox"/> Newspaper |
| <input type="checkbox"/> Departmental/Center Newsletters | <input checked="" type="checkbox"/> Web-Based Clinical Trial Registries | |
| <input type="checkbox"/> YCCI Recruitment database | <input checked="" type="checkbox"/> Clinicaltrials.gov Registry (do not send materials to HIC) | |
| <input type="checkbox"/> Other (describe): | | |

3. Recruitment Procedures:

- a. Describe how potential subjects will be identified.

Adults age 18 and older presenting to the ED with femoral neck and intertrochanteric femur fractures

- b. Describe how potential subjects are contacted.

Patients will be approached in the ED

- c. Who is recruiting potential subjects?

Principal investigator and orthopedic consult residents

4. Screening Procedures

- a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? Yes No
- b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

Names

All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains

more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

- Telephone numbers
 Fax numbers
 E-mail addresses
 Social Security numbers
 Medical record numbers
 Health plan beneficiary numbers
 Account numbers
 All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
 Certificate/license numbers
 Vehicle identifiers and serial numbers, including license plate numbers
 Device identifiers and serial numbers
 Web Universal Resource Locators (URLs)
 Internet Protocol (IP) address numbers
 Biometric identifiers, including finger and voice prints
 Full face photographic images and any comparable images
 Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

- Yes, all subjects
 Yes, some of the subjects
 No

If yes, describe the nature of this relationship.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

- For entire study
 For recruitment purposes only
 For inclusion of non-English speaking subject if short form is being used
- i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
 - ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the “accounting for disclosures log”, by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

- 7. Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

Compound Consent and Authorization form
 HIPAA Research Authorization Form

- 8. Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

Michael P. Leslie, DO
Adrian Wyllie, MD
Stephen Nelson, MD
Daniel Wiznia, MD

- 9. Process of Consent/Accent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

The process of consent will be confidential and discussed in a private setting, and the patient will have time to think or discuss with family member(s). The informed consent form will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The informed consent form contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study. The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated consent form and will document in the subject's source notes that informed consent was given.

10. Evaluation of Subject(s) Capacity to Provide Informed Consent/Accent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

If the person has the capacity to consent for the operative treatment, they are able to consent for the study as well.

11. Documentation of Consent/Accent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Will attach consent form

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

A Spanish Form of the consent as well as informed consent explained through either a medical translator or translator phone services.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?

YES NO

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at:

<http://www.yale.edu/hrpp/forms-templates/biomedical.html>. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

X Not Requesting a consent waiver

- Requesting a waiver of signed consent
 Requesting a full waiver of consent

A. Waiver of signed consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

- Requesting a waiver of signed consent for Recruitment/Screening only

If requesting a waiver of signed consent, please address the following:

- a. Would the signed consent form be the only record linking the subject and the research?
 Yes No
- b. Does a breach of confidentiality constitute the principal risk to subjects?
 Yes No

OR

- c. Does the research activity pose greater than minimal risk?

Yes **If you answered yes, stop. A waiver cannot be granted.** Please note:

Recruitment/screening is generally a minimal risk research activity

X No

AND

- d. Does the research include any activities that would require signed consent in a non-research context? Yes No

- Requesting a waiver of signed consent for the Entire Study (Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

- a. Would the signed consent form be the only record linking the subject and the research?
 Yes No
- b. Does a breach of confidentiality constitute the principal risk to subjects?
 Yes No

OR

- c. Does the research pose greater than minimal risk? Yes **If you answered yes, stop. A waiver cannot be granted.** **X No**

AND

- d. Does the research include any activities that would require signed consent in a non-research context? Yes No

B. Full waiver of consent: (No consent from subjects will be obtained for the activity.)

- Requesting a waiver of consent for Recruitment/Screening only

- a. Does the research activity pose greater than minimal risk to subjects?

- Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note:
Recruitment/screening is generally a minimal risk research activity
 No
b. Will the waiver adversely affect subjects' rights and welfare? Yes No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

- Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

- a. Does the research pose greater than minimal risk to subjects?
 Yes ***If you answered yes, stop. A waiver cannot be granted.***
 No
b. Will the waiver adversely affect subjects' rights and welfare? Yes No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

- a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Medical record numbers, social security numbers, telephone numbers, medical history, age, date of birth.

- b. How will the research data be collected, recorded and stored?

Research data will be collected by interviewing the subject or the power of attorney, questionnaires. The data will be recorded and stored electronically on a password-protected computer. The research data will also be stored on a flash drive, portable hard drive and kept locked in the PI's office.

- c. How will the digital data be stored? CD DVD X Flash Drive X Portable Hard Drive X Secured Server X Laptop Computer Desktop Computer Other

- d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

The PI's password-protected computer will store the collected data and an encrypted portable hard drive and a flash drive will be used for data transport. These materials will be stored in the PI's locked office.

Do all portable devices contain encryption software? X Yes No

If no, see <http://hipaa.yale.edu/guidance/policy.html>

- e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Upon the completion of this study, collected data will be saved in an encrypted portable hard drive stored in a locked cabinet in the PI's locked office for use for possible follow-up studies. After all studies have been completed, all stored data will be destroyed by the PI using secure erase.

- f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

The research team at Yale New Haven Hospital will be the only ones to have access to the de-identified information.

- g. If appropriate, has a [Certificate of Confidentiality](#) been obtained? N/A

- h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.
NO

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The potential benefits include decreased morbidity and possible mortality in intertrochanteric femur fractures. With decreased bleeding preoperatively and postoperatively, the likelihood of wound problems, infection, or post-operative hematomas will be much less. In addition, the morbidity and mortality from a allogeneic transfusion will be decreased if TXA is used. Lastly, health care costs will be decreased, as transfusions are costly interventions, compared to the cost of TXA (\$41 per dose vs > \$400 for an allogeneic transfusion of packed red blood cells.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation. **None**
2. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

The cost to the patient will be zero. The drug itself costs \$17.00.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
 - a. Will medical treatment be available if research-related injury occurs?
The patient will have full access to medical care while in the hospital and post operatively.
 - b. Where and from whom may treatment be obtained?
The attending physician (PI) and any other consulting physicians that are needed.
 - c. Are there any limits to the treatment being provided? **NO**
 - d. Who will pay for this treatment?
The subject or the subject insurance is responsible for the financial cost.

- e. How will the medical treatment be accessed by subjects?

Through YNNH in the post operative period