1. Title of the Study

Topical (*Intra-Articular*) Tranexamic Acid and Transfusion Rates Following Hip Hemiarthroplasty

Principal Investigator's Name & Contact Information:

Vincent Williams, MD

Assistant Professor Department of Orthopaedic Surgery

University of Connecticut Health Center

263 Farmington Ave., Farmington, CT. 06030

vwilliams@uchc.edu (860) 679-8384

Co-Investigators:

Michael O'Sullivan MD (Orthopaedic Surgery Resident)

Mark P. Cote PT, DPT, MSCTR Department of Orthopaedic Surgery

Collaborating Sites:

St. Francis Medical Center

114 Woodland St.

Hartford, CT.

Site Principal Investigator:

Jeffery Meter, MD

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2. Background

Packed red blood cell transfusion is associated with the risk of infection (HIV, hepatitis B virus, hepatitis C virus, human T-lymphotropic virus type 1 and 2, cytomegalovirus, bacteria), immunosuppression, hemolysis, fever, urticaria, allergic reaction, and even death [1]. In addition to these risks, packed red blood cell transfusion increases hospitalization costs and has the potential to increase hospital stay. At UCHC, one unit of packed red blood cells typically costs $300-400, but may cost as much as $1,000. Because of these risks and costs, investigators have sought methods to decrease the need for packed red blood cell transfusion including the use of tranexamic acid.

Tranexamic acid is a derivative of the amino acid lysine. This drug works to decrease blood loss through its interaction with fibrin. The drug competitively and reversibly binds to the lysine binding sites of fibrin. This prevents plasminogen and its enzymatically active form, plasmin, from binding to fibrin. By preventing plasminogen/plasmin from binding fibrin, tranexamic acid prevents enzymatic degradation of the fibrin clot. Tranexamic acid, therefore, stabilizes the fibrin clot by shifting the local balance of fibrinolysis/coagulation toward coagulation leading to decreased blood loss. The drug has a half-life of 1-2 hours [2]. At UCHC, one gram of tranexamic acid typically costs $40-41.

Intravenous tranexamic acid reduces blood loss and packed red blood cell transfusion requirements when used during surgery. Yang et al. performed a meta-analysis of randomized control trials evaluating the use of tranexamic acid use in total knee arthroplasty. Their analysis included 15 randomized control trials comprised of 837 patients. They found the mean difference in blood loss between the patients receiving tranexamic acid and those receiving placebo was -504.9 ml (95% CI, -620.89 to -388.92 ml; $p < 0.00001$). The number of packed red blood cell transfusions per patient was also significantly less in the patients receiving tranexamic acid (weighted mean difference -1.43 units; 95% CI, -1.69 to -1.17 units; $p < 0.00001$) [3]. Henry et al. showed that tranexamic acid use in elective surgery reduced the need for packed red blood cell transfusion by 39% (RR 0.61; 95% CI, 0.53-0.70) in their review of 65 randomized control trials including 4842 patients. This reduction corresponds with an absolute risk reduction of 18% (95% CI, -0.22 to -0.14) [4].

Intravenous tranexamic acid use has not been associated with increased incidence of complications. Henry et al. evaluated the relative risk of complications with tranexamic acid use in the randomized control trials they reviewed. Tranexamic acid use did not increase the relative risk of mortality (RR 0.60, 95% CI, 0.33 to 1.10) in 30 randomized control trials involving 2917 patients. Use

of the drug was not associated with increased risk of myocardial infarction (RR 0.79, 95% CI, 0.41 to 1.52) in 21 randomized control trials involving 2186 patients. Tranexamic acid use was not associated with a statistically significant increase in stroke (RR 1.23, 95% CI 0.49 to 3.07) in 18 randomized control trials including 2027 patients. Use of the drug, also, was not associated with an increased risk for a deep vein thrombosis (RR 0.71, 95% CI 0.35 to 1.43) in 23 randomized control trials including 1472 patients. Additionally, tranexamic acid use did not increase the relative risk for suffering a pulmonary embolism (RR 0.67, 95% CI 0.23 to 1.99) in 14 randomized control trials including 1006 patients. Finally, tranexamic acid did not increase the relative risk of renal failure/dysfunction (RR 0.89, 95% CI 0.33 to 2.37) in 9 randomized control trials including 912 patients [4]. Yang et al., also, demonstrated that tranexamic acid use was not associated with an increased risk of complications. Use of the drug was not associated with an increased rate of deep vein thrombosis (DVT) (OR 0.75, 95% CI 0.34 to 1.67; p = 0.48) in 13 randomized control trials including 722 patients or an increased rate of pulmonary embolism (OR 0.65, 95% CI 0.18 to 2.33; p = 0.50) in 6 randomized control trials involving 349 patients. Additionally, tranexamic acid use did not alter the prothrombin time (mean difference -0.04 seconds, 95% CI -0.33 to 0.24 seconds; p = 0.77) in 4 randomized control trials documenting this data or the activated partial thromboplastin time (mean difference 0.37 seconds, 95% CI, -0.56 to 1.29 seconds; p = 0.44) in 5 randomized control trials [3].

Tranexamic acid can also be delivered topically rather than intravenously. De Bonis et al. demonstrated that tranexamic, when delivered topically, was not detected in the blood stream of 24 patients undergoing coronary artery bypass surgery [5]. Giving the drug in this fashion both concentrates the drug at the desired location and diminishes or even prevents systemic absorption and therefore any potentially detrimental thrombotic complications. Ker et al. demonstrated that topical delivery of tranexamic acid reduced the risk of packed red blood cell transfusion by 45% (RR 0.55; 95% CI, 0.46-0.65; p < 0.0001) and the risk of blood loss by 29% (RR 0.71; 95% CI, 0.69-0.72; p < 0.0001) in their meta-analysis including 29 randomized control trials and 2612 patients. They also demonstrated that topical use of the drug was not associated with an increased rate of complications. Topical use of the drug was associated with a the risk of relative risk of 0.28 (95% CI, 0.06-1.34; P = 0.11) for mortality, 0.33 (95% CI, 0.04-3.08; P = 0.33) for myocardial infarction, 0.33 (95% CI, 0.01-7.96; P = 0.49) for stroke, 0.69 (95% CI, 0.31-1.57; P = 0.38) for DVT, and 0.52 (95% CI, 0.09-3.15; P = 0.48) for pulmonary embolism [6].

In the TRANX-K and TRANX-H studies, Alshryda et al. tested the use of topical tranexamic acid in both total knee arthroplasty and total hip arthroplasty respectively. The TRANX-K study was a randomized, placebo-controlled trial including 157 patients undergoing total knee arthroplasty who received either 1-gram tranexamic acid diluted with 50 cc saline intra-articularly or a placebo. With the use of the drug, they were able to reduce the risk of packed red blood cell transfusion from 16.7% to 1.3%, representing an absolute risk reduction of 15.4%. Use of the drug was associated with a decrease in hospital stay by 1.2 days (95% CI, 0.05 to 2.43 days; p = 0.041) and cost per patient by £333 (95% CI, £37 to £630; p = 0.028). There were no significant differences between study groups with respect to complications, though the study was not powered to detect a difference [7]. The TRANX-H study was a randomized, placebo-controlled trial including 161 patients undergoing a primary total hip arthroplasty who received either 1 gram tranexamic acid diluted with 50 cc of saline intra-articularly or a placebo. With the use of tranexamic acid, they were able to reduce their packed red blood cell transfusion rate from 32.1% to 12.5%, representing an absolute risk reduction of 19.6%. Topical use of the drug was associated with a decrease in hospital stay by 1.0 days (95% CI, -0.2 to 2.3 days; p = 0.109) and cost per patient by £305 (95% CI, £0 to £610; p = 0.05). There were no significant differences between study groups with respect to complications, though the study was not powered to detect a difference [8].

Seo et al. demonstrated that topical delivery of tranexamic acid was more effective than intravenous (IV) administration for preventing packed red blood cell transfusion in their randomized, placebo-controlled trial of 150 patients. In this trial, 50 patients received tranexamic acid IV, 50 patients received tranexamic acid intra-articularly, and 50 patients received placebo. Blood loss was 528 +/- 227, 426 +/- 197, and 833 +/- 412 ml for the groups respectively with statistically significant inter-group differences ($p < 0.001$). Packed red blood cell transfusion rates were 34%, 20%, and 94% ($p < 0.001$) respectively. There were no statistically significant differences in complication rates [9].

Because topically applied tranexamic acid reduces the need for packed red blood cell transfusion and does not appear to increase the risk of complication, we wish to study the use of this drug in patients undergoing hip hemiarthroplasty for femoral neck fracture. Femoral neck fractures are a pattern of hip fractures that predominantly occur in an elderly population. The average age of patients sustaining a femoral neck fracture is 79 for women and 74.3 for men [10]. The incidence has been reported as 63.3 per 100,000 person years in woman and 27.7 per 100,000 person years in men [11].

Femoral Neck fractures are associated with high rates of avascular necrosis of the femoral head due to disruption of the lateral epiphyseal artery, a branch of the medial femoral circumflex artery which

accounts for the majority of blood supply to the femoral head, with displacement of the fracture. Because of the high rates of AVN with fracture displacement and the advanced age of most patients presenting with this fracture pattern, often a decision is made to preform a hip hemiarthroplasty. Alternatives to hemiarthroplasty include open reduction internal fixation, which is typically reserved for younger patients when there is a desire to preserve the femoral head, and total hip arthroplasty, which is typically reserved for patients with a high level of pre-injury function. A hip hemiarthroplasty involves removing the femoral neck and head, inserting a femoral stem that is either cemented or press-fit into the intramedullary cavity of the femur, and replacing the femoral neck and head. In a hip hemiarthroplasty, the native acetabulum is left intact whereas in a total hip replacement the acetabulum is reamed to a bleeding bone base and a press fit acetabular cup is impacted to complete replacement of this bony surface.

Since the native acetabulum is left intact in a hemiarthroplasty, one might assume that a hemiarthroplasty is associated with less blood loss than a total hip replacement. Van den Bekerom et al. showed that hemiarthroplasty was associated with decreased intra-operative blood loss compared with total hip arthroplasty. In this study, 8 of 137 patients receiving hemiarthroplasty had an intra-operative blood loss greater than 500 cc, while 25 out of 115 patients receiving total hip arthroplasty had an intra-operative blood loss greater than 500 cc [12].

Literature regarding packed red blood cell transfusion rates in patients receiving hemiarthroplasty is sparse. Parker et al. reported a packed red blood cell transfusion amount of 0.39 units per patient in a randomized clinical trial involving 223 patients receiving hemiarthroplasty [13]. Kadar et al. reported that 270 out of 579 patients receiving hemiarthroplasty for femoral neck fracture required a packed red blood cell transfusion for a rate of 46.6% [14]. Rogmark et al. demonstrated that 85 of 103 (82.5%) patients receiving hemiarthroplasty for a femoral neck fracture required packed red blood cell transfusion. Of these patients, 32 (31.1% of all hemiarthroplasty patients) required 3 or more units [15].

A literature review using Pubmed and the search terms “tranexamic acid” and “hemiarthroplasty” does not reveal any results. Though we were unable to detect any prior studies in which tranexamic acid was used for hemiarthroplasty of the hip, this procedure is very similar to a total hip arthroplasty. Though hemiarthroplasty is associated with less blood loss than a total hip arthroplasty, the patients receiving a hemiarthroplasty are typically older and have more medical comorbidities. Therefore, these patients have a lower threshold to undergo packed red blood cell

transfusion. Given these offsetting factors, we believe the use of topical tranexamic acid in patients undergoing hemiarthroplasty may show similar benefits in reducing packed red blood cell transfusion rates and therefore increasing patient safety and decreasing medical costs.

3. Hypotheses, aims and objectives:

Hypothesis: Topically applied tranexamic acid will demonstrate a statistically significant reduction in packed red blood cell transfusion requirements when administered to patients undergoing hip hemiarthroplasty in comparison to a placebo control.

Aims / objectives: The goal of the research is to demonstrate that topical tranexamic acid can potentially decrease packed red blood cell transfusion requirements in patients undergoing hip hemiarthroplasty, thus improving patient safety and decreasing medical costs. We will achieve this aim by measuring packed red blood cell transfusion rates, packed red blood cell transfusion amounts, and overall medical cost per admission for both study arms.

4. Study Design & Procedures:

- *Study design:* Double Blinded, Randomized Placebo-Controlled Trial
- *Screening Procedures and who will perform them:*

  Patients will be screened for eligibility when they are scheduled to undergo a hip hemiarthroplasty. This cohort consists of patients who present to the emergency department with a femoral neck fracture requiring operative intervention. Screening will consist of a review of the patients' medical history. Prior to screening, verbal consent will be obtained to allow the patient's medical record to be reviewed to determine eligibility. Specifically, patients will be informed about the study by the attending or resident on call and asked whether they are interested in learning more. If the patient is interested, permission for a member of the study team to review their medical record will be sought and documented in the medical record. The information obtained during this screening is also obtained as part of the required work up for patients undergoing operative intervention. If a patient is deemed eligible, they will be offered

enrollment into the study and will undergo informed consent. In the event of a screen failure, only year, age, gender, and the reason for exclusion will be recorded on a formal screening log. For screen failures whose age is 90 or greater, the specific age will not be recorded but rather noted as "90+" on the screening log. The PI, Co-Investigator Michael O'Sullivan, or the orthopedic surgery resident that is on call during the time of admission will be a part of all screening procedures. Each year there is a resident who has one year dedicated to research between their post graduate year 2 and year 3 with time available to dedicated specifically to this project. To ensure that all eligible patients are screened and if appropriate consented, orthopedic surgery residents who take call will be added to the IRB application as consenters following completion of the attached "Educational Plan For Consenters" as necessary. Only those residents with completed training who have been added to the study and have been approved by the IRB will be allowed to obtain consent for study participation.

- *Study Procedures and who will perform them:*

Prior to the start of the study, a randomization schedule will be constructed with block randomization using web-based software. Patients will then be allocated to one of two groups: Topical tranexamic acid or Placebo (saline). Group assignments will be concealed in opaque sealed envelopes with a numerical code of consecutive numbers reflecting patient enrollment. Envelopes will be stored with the pharmacy staff in charge of drug preparation. The pharmacy staff, which will have no patient contact, will remain un-blinded. The pharmacy staff will maintain the master key identifying which patients received the study drug and which patients received the placebo. Physicians, residents, hospital staff, and patients will be blinded to group assignment.

Eligible patients will be offered study enrollment following the screening protocol documented above in the "Screening procedures and who will perform them" section. The PI, Co-Investigator, Michael O'Sullivan, or the orthopedic surgery resident that is on call during the time of the patients' hospital admission will obtain informed consent using the informed consent form approved by the IRB. Before a resident can serve as a consenter, he or she must first complete the training protocol found on the form "Educational Plan For Consenters."

Patients recruited in the Emergency Department or the hospital floor may be in pain, upset about the circumstances that brought them there, confused by what is being done to them, and frightened about what is going to come next. In order to avoid exerting undue pressure on these patients, an "Educational Plan for Consenters" was developed. This plan includes a PowerPoint presentation outlining ethics in research, guiding moral principles, and issues surrounding informed consent as well as two papers for each investigator to read prior to consenting patients. The first paper, provided by the National Institutes of Health Clinical Center Department of Bioethics, reviews how to treat people participating in research. The second paper is a study appearing in the BMC journal of Medical Ethics in which the authors conducted a systematic review of randomized controlled trials testing interventions in an effort to analyze the informed consent processes. This review provided the authors with a platform to discuss methods to improve the consent process, specifically patient understanding. Together, these two papers and presentation highlight, among other things, the importance of recognizing the stressful situation patients may find themselves in when being approached for study participation. They also provide strategies to monitor undue pressure on patients who may be especially vulnerable. Prior to becoming a consenter for the study, each investigator will read and review both papers and view the PowerPoint presentation. Upon completion, the potential issues specific to this study (approaching patients with very recent hip fractures in the Emergency Department or on the hospital floor for study participation) will be discussed with Mark Cote, who is not a consenter for this study. A completion form will be kept on file for consenters.

Informed consent for study inclusion will be obtained after informed consent for the surgical procedure, a hip hemiarthroplasty, has been obtained. In order to provide informed consent for the surgical procedure, a hip hemiarthroplasty, a patient must demonstrate understanding of their diagnosis, the proposed surgical procedure, the risks and benefits of this surgical procedure, the risks and benefits associated with alternative treatment modalities, and wish to undergo a hip hemiarthroplasty. Informed consent for study inclusion will be sought from the patient following consent for their surgical procedure. In some instances, informed consent for surgery is obtained from a legally authorized representative (LAR) because the patient is decisionally impaired. If a patient is unable to provide his or her own consent for surgery and requires a legally authorized representative, we will obtain informed consent for study participation from this legally authorized representative (LAR) once we are able to obtain written proof of the LAR status. In

this scenario, assent will be sought from the patients. Considering that decisionally impaired adults are part of the population to which the results of this study are intended to benefit, we do not want to exclude them based solely on their mental incapacity. There may be instances where a patient is able to consent for surgery but doesn't understand the research. If during the consent process there is any question regarding the patient's capability to understand the research and provide informed consent as evidence by an inability to describe the elements of the study, a screening tool provided with this submission will be used to assess the patient's mental capacity. The University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) is a tool for assessing decisional capacity for clinical research [22]. It was designed as an extension of a 3-item questionnaire to include a more comprehensive assessment of understanding, appreciation, and reasoning about protocol elements that are essential for obtaining informed consent. There are 10 items on the UBACC that ask the respondent to state main details of the study as well as elements and implications of participation. Each of the 10 items on the UBACC is scored as 2 (correct), 1 (some deviation from correct) and 0 (incorrect). A cut-off of 14.5 has been shown to discriminate between those who are and those who are not capable of providing consent when compared to the opinion of an expert reviewer [22]. For this study a cut-off of 16 will be used to in an effort to ensure only those who are decisional capable are permitted to provide informed consent. A score of less than 16 will constitute a decisional impairment. In this instance (score less than 16), consent will be sought from the LAR and assent will be sought from the patient. In order to be included in the study, decisionally impaired individuals must have a documented LAR who provides informed consent and the decisionally impaired individiual must provide assent. If either of these circumstances is not met, the decisionally impaired individual will represent a screening failure.

Documentation of LAR status is required before an individual can provide informed consent for a surgical intervention on a decisionally impaired individual under this designation. If an LAR is unable to initially provide this documentation prior to the surgical intervention, the surgical intervention is delayed until the LAR can obtain this documentation. If the LAR definitively cannot produce this documentation, then informed consent is sought from the patient's "next of kin." If the "next of kin" provides informed consent for the surgical intervention for a decisionally impaired individual, this patient will be excluded from study enrollment and

represent a screening failure. As such, documentation of LAR status will be readily obtainable because the orthopaedic service requires this documentation prior to surgical intervention.

The informed consent process will occur either in the emergency department or on the inpatient floor. The investigator will limit any outside distractions during this time (i.e. closing doors, turning off TVs, etc.). The informed consent procedure will include a thorough review of the informed consent document. If a patient or LAR is unable or unwilling to review this document for any reason, the informed consent process will terminate in accordance with the patient/LAR's wishes and the patient will be excluded from the study. The investigator will attempt to answer any question the patient or LAR may have regarding study inclusion. If the investigator is unable to answer a particular question, this answer will be sought prior to patient enrollment. If a particular question is unable to be answered, the investigator will convey this information truthfully.

If an LAR is required to provide informed consent, obtaining informed consent from the LAR and assent from the patient will occur in the patient's room with both the patient and LAR present so that communication regarding the study is not withheld from the patient despite his or her decisional impairment. If the LAR is not in the hospital, the LAR will be contacted in the manner that the orthopaedic surgery service contacted the LAR (e.g. by phone). If the LAR indicates that he or she is planning on coming to the hospital prior to the surgical intervention, informed consent for study inclusion will be sought at this time so that a face-to-face consent process can occur. If the LAR does not plan to come to the hospital before the surgical intervention or the LAR is unable to come to the hospital, the patient will not be eligible for study inclusion.

Once informed consent is obtained, the pharmacy will be contacted to allow provision of the study drug at the time of the procedure. When the patient is brought to the operating room, the pharmacy staff will open the numerical envelope assigned for the specific patient. The patient will undergo a hip hemiarthroplasty, according to the standard of care for a displaced femoral neck fracture. Surgical approach and implant selection will be left to the discretion of the attending surgeon. The only difference associated with study participation is that prior to wound closure, either a resident performing the surgery or the attending physician will introduce 1 gram

of tranexamic acid (APP Pharmaceuticals LLC, Schaumburg, IL) mixed with normal saline (0.9% NaCl) for a total volume of 50 cc or a 50 cc normal saline placebo into the wound. Of the 50 cc of the study drug or placebo, 25 cc will be introduced intra-articularly and 25 cc will be introduced under the fascial layer. When introducing either the study drug or placebo, the resident or attending physician should attempt to coat all surfaces with a thin layer of the aqueous solution. Wound closure technique will be left to the discretion of the attending surgeon. Post-operative venous thromboembolic prophylaxis will be left to the discretion of the attending surgeon.

Following surgery, the patient will be admitted to the hospital per the standard of care. The length of inpatient stay following this procedure is approximately 3 to 4 days, however this may vary. Following discharge from the hospital, patients will follow up with the treating surgeon at two outpatient visits (one at approximately 2 weeks, a second at 4-6 weeks). These visits are the regularly scheduled post-operative visits as part of routine care. The methods and types of data to be collected are described in the "Methods of Data Collection" section of this protocol.

- *Sample size and justification:*

A sample size calculation was conducted to determine the number of patients needed to observe a difference in packed red blood cell transfusion rates. In the last two fiscal years at UCHC a hip hemiarthroplasty has been performed in 84 patients, 29 of which required packed red blood cell transfusions (34.5%). We queried the Health Care Utilization Project Database, a stratified 20% national sample of over 7,000,000 hospital stays at over 1,000 hospitals in 46 states, to estimate national rates of packed red blood cell transfusion. In this sample, 14,813 of 45,800 (32.3%) patients undergoing hip hemiarthroplasty in 2011 required a packed red blood cell transfusion. Given these numbers, we used a value for packed red blood cell transfusion rate of 35% for patients that receive placebo. The literature has shown packed red blood cell transfusion rates with use of the drug in an orthopedic setting in similar populations to range from 12.5% to 1%. Accordingly, we selected a packed red blood cell transfusion rate of 10% in patients receiving tranexamic acid. A two group continuity corrected Chi square test with a 0.05 two-sided significance level will have 80% power to detect the difference between packed red blood cell

transfusion rates of 35% and 10% (odds ratio of 4.846) when the sample size in each group is 51 (102 total).

- *Explain on what basis it is reasonable to assume that the sample size will be obtained:*

  The number of hip hemiarthroplasties performed annually has been increasing. In the last fiscal year, 49 hip hemiarthroplasties were performed at UCHC. With a 2-year study period and the possibility that the study may be extended to neighboring facilities (St. Francis Medical Center), it is reasonable to assume the sample size will be obtained.

- *Subject characteristics and justifications:*
  - Age: Over 55 years.
  - Ethnicity: No restrictions.
  - Gender: No restrictions.
  - Vulnerable Populations:

    This population includes patients with fragility fractures. A small percentage of this group has decisional impairment and will require consent from a health care proxy for operative intervention. In these instances, the legally authorized representative (LAR) as determined by documentation court-appointed conservator or guardian, power of attorney for health care, or an individual designated as a health care representative, will provide consent if the patient is deemed eligible. Documentation of the LAR status will kept on file. If the LAR cannot provide documentation, the patient will not be included in the study. The process of obtaining consent is detailed in the "Study procedures and who will perform them" section of this protocol.
  - Other characteristics - (e.g. vulnerable populations; primary language etc.):

    If a patient cannot speak English, they will be excluded from the study.

- *Inclusion Criteria:*

  Patients undergoing hip hemiarthroplasty for a displaced femoral neck fracture will be included.

- *Exclusion criteria:*

Comorbid Conditions – Patients with a history of hemophilia, deep vein thrombosis, pulmonary embolism, thrombophilia, and chronic renal failure will be excluded. Patients with recent (i.e. within the past calendar year) or active coronary ischemia will be excluded. Patients who have suffered a myocardial infarction, undergone percutaneous coronary intervention, undergone coronary artery bypass grafting, or undergone any revascularization procedure within the past calendar year will be excluded. Patients with an active subarachnoid hemorrhage, acquired defective color vision, patients who sustained a pathological fracture (fracture through a neoplastic lesion), or patients who are pregnant will be excluded. Finally, patients with a known allergy to tranexamic acid will be excluded.

Therapeutics – Patients taking the following therapeutics will be excluded:

- Warfarin
- Dabigatran
- Rivaroxaban
- Apixaban
- Fresh Frozen Plasma

Warfarin requires reversal prior to surgery. Because there are multiple methods to achieve reversal from the elevated INR associated with warfarin use, which have different impacts on potential intra-operative and post-operative blood loss, inclusion of this population is not feasible. Dabigatran, rivaroxaban, and apixaban use constitutes exclusion because these drugs are relatively rare leading to potential imbalance of study groups and their effect on bleeding has not been adequately investigated in the literature. Because these drugs are relatively new, there is controversy associated with surgical timing when patients are taking these medications. Some providers elect to wait up to 48 hours since the last dose, while others operate immediately. There is no formal lab value that can monitor these drugs' impact on coagulation. As such, we have excluded these drugs.

Patients on anti-platelet medication (aspirin, clopidogrel, etc.) will be included in this study. Please refer to the protocol attachment "Anti-platelet Rationale" for a complete explanation. Use of these medications will be recorded as a covariate for analysis.

Because patients sustaining femoral neck fractures rarely undergo surgical intervention in the same day, they are typically given a dose of either enoxaparin or heparin upon admission to prevent deep vein thrombosis given their injury and immobility. Patients receive this medication each day until the day of their surgical intervention, at which time this medication is held to prevent excessive intra-operative blood loss. The drug is resumed on post-operative day 1 for deep vein thrombosis prophylaxis. The drug insert for enoxaparin states, "significant anti-factor Xa activity persists for 12 hours following a 40 mg subcutaneous once a day dosing." Because this medication is held on the day of surgery, there is greater than 12 hours from the last dose received until the surgical intervention. Patients who receive either enoxaparin or heparin will be included in the study. We will record the use of these medications (e.g. enoxaparin and heparin) and the interval between the last dose of medication and the surgical intervention for covariate analysis. Given how common the in-hospital use of these medications is in patients prior to undergoing hip hemiarthroplasty, we expect to achieve balanced groups through the process of randomization. Coagulation labs (PT/PTT/INR), when obtained prior to surgery, will be recorded to demonstrate similarity between the groups.

- *Describe length of subject's participation in the study including number of visits, frequency of visits, and length of visits:*

  Patients will be in the study for 4 to 6 weeks. This time period will encompass their inpatient hospital stay and their first two outpatient visits (one at approximately 2 weeks, a second at 4-6 weeks). These visits are the regularly scheduled post-operative visits that are part of routine care follow up. No extra time per visit or number of visits will be required as a result of study inclusion. The scheduled date of the patient's post-operative outpatient visit occurring between 4 and 6 weeks will reflect the last day of study involvement.

- *Methods of Data Collection and Types of Data to be collected:*

  All data will be collected using an IRB approved data collection form. Data will consist of demographic information (age, gender, body mass index, injury side, comorbidities, etc.), pre- and postoperative blood values (hematocrit/hemoglobin, PT/PTT/INR (if obtained), etc.), pre-operative anti-platelet use (aspirin, etc.), pre-operative heparin or enoxaparin use and interval between last dose and the surgical procedure, time from admission to surgical intervention, intra-

operative details (approach, cemented vs. un-cemented, surgeon, operative time, anesthesia, and estimated blood loss), packed red blood cell transfusion rates and amount, length of inpatient stay, prescribed chemoprophylaxis, complications (transfusion related complications, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, death, infection, hematoma), and inpatient cost. Detailed list of the data to be collected as well as time points of collection can be found in the attachment to this labeled "Data Collection Forms."

The primary outcome measure is the rate of packed red blood cell transfusion. Secondary outcome measures include amount of packed red blood cell transfusion, difference between pre- and postoperative hemoglobin/hematocrit, length of stay, complications, and inpatient cost.

The study staff (principal investigator, research coordinator, co-investigators etc.) will keep all study records (including any codes to patient data) locked in a secure location. Research records will be labeled with a code and all contents of the research record will be labeled with only that code. The code will be derived from the patient's first and last initial followed by a sequential 3-digit number that reflects how many people have enrolled in the study. A master key that links names and codes will be maintained in a separate and secure location. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected. The consent form will be stored separate from the research file in a secure location. A copy of the consent will be kept in the medical record to inform other providers who may become involved in caring for the patient that they are enrolled in this study. By adding the consent to the medical record others, including additional healthcare providers and the patient's insurer, may become aware of their participation in this study. Additionally, a copy of the consent will be provided to the pharmacy to ensure that the drug is properly dispensed to study patients. Any computer hosting such files will also have password protection to prevent access by un-authorized users. Data that will be shared with others will be coded as described above to help protect patient identity.

- *Method(s) of data analysis:*

  Descriptive summary statistics to characterize the two groups such as means and standard deviations for numeric data and proportions for categorical data will be calculated where appropriate. Difference in the primary outcome measure, rate of packed red blood cell

transfusion, will be analyzed using a two-group continuity corrected Chi-square test. Differences in packed red blood cell transfusion rates, amount of blood transfused, and inpatient cost will be analyzed using a two-group *t* test. Regression analysis will be used to model packed red blood cell transfusion outcomes against the main predictors (group allocation), adjusting for the effect of covariates (comorbidities, post-operative venous thromboembolism prophylaxis, etc.). Specifically, logistic regression will be used to model packed red blood cell transfusion as a binary outcome (yes or no) and multiple linear regression will be used to model packed red blood cell transfusion amounts and rates. The alpha level for all statistics will be set at 0.05.

5. Timetable

- Expected Start Date: 11/1/15
- General Time Table**:** 2 years
- Expected Completion Date: 10/31/17

6. Budget / resources:

We have received a Resident Research Project grant award from the Orthopaedic Research and Education Foundation (OREF). The pharmacy, which will play an essential role in this project, has been appropriately budgeted and is available to participate in this study.

7. Dissemination

We plan to disseminate the results of our research in the form of a peer reviewed journal article as well as application for presentation at a national society meetings.

8. References / Literature Review:

1. Keating EM, Meding JB. Perioperative Blood Management Practices in Elective Orthopaedic Surgery (Review). *J Am Acad Orthop Surg.* 2002;10(6):393-400.

2. Eubanks JD. Antifibrinolytics in Major Orthopaedic Surgery (Review). *J Am Acad Orthop Surg.* 2010;18(3):132-8.

3. 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(13):1153-1159.

4. Henry DA, Carless PA, Moxey AJ, O'Connell D, Strokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimizing perioperative allogenic blood transfusion. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.:CD001886. DOI:10.1002/14651858.CD001886.pub4.

5. De Bonis M, Cavaliere F, Alessandrini F, Lapenna E, Santarelli F, Moscato U, Schiavello R, Possati GF. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *J Thorac Cardiovasc Surg.* 2000;119(3):575-80.

6. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD010562. DOI: 10.1002/14651858.CD010562.pub2.

7. Alshryda S, Mason J, Vaghela M, Sarda P, Nargol A, Mahewsaran S, Tulloch C, Anand S, Logishetty R, Stothart B, Hungin APS. Topical (Intra-Articular) Tranexamic Acid Reduces Blood Loss and Transfusion Rates Following Total Knee Replacement, *J Bone Joint Surg Am*. 2013;95:1961-8.

8. Alshryda S, Mason J, Sarda P, Nargol A, Cooke N, Ahmad H, Logishetty R, Vaghela M, McPartlin L, Hungin APS. Topical (Intra-Articular) Tranexamic Acid Reduces Blood Loss and Transfusion Rates Following Total Hip Replacement, *J Bone Joint Surg Am.* 2013;95:1969-74.

9. Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(8):1869-1874.

10. Horiuchi T, Igarashi M, Karube S, et al. Spontaneous fractures of the hip in the elderly. Orthopedics 1988;11:1277-1280.

11. Koval KJ, Zuckerman JD: Hip fractures: I. Overview and evaluation and treatment of femoral-neck fractures. *J Am Acad Orthop Surg.* 1994;2:141-9.

12. Van den Bekerom MPJ, Hilverdink EF, Sierevelt IN, Reuling EMBP, Schnater JM, Bonke H, Goslings JC, van Dijk CN, Raaymakers ELFB. A comparison of hemiarthroplasty with total hip replacement for displaced intracapsular fracture of the femoral neck: a randomized controlled multicenter trial in patients aged 70 years and over. *J Bone Joint Surg Br.* 2010;92-B(10):1422-1428.

13. Parker MJ, Khan JK, Crawford GA. Hemiarthroplasty versus internal fixation for displaced intracapsular hip fractures in the elderly: A randomized trial of 455 patients. *J Bone Joint Surg Br.* 2002;84-B;1150-5.

14. Kadar A, Chechik O, Steinberg E, Reider E, Sternheim A. Predicting the need for blood transfusion in patients with hip fractures. *Int Orthop* 2013;37(4):693-700.

15. Rogmark C, Carlsson A, Johnell O, Sernbo I. Primary hemiarthroplasty in old patients with displaced femoral neck fracture. *Acta Orthop Scand*. 2002;73(6):605-610.

16. Parvizi J, Ereth MH, Lewallen DG. Thirty-day mortality following hip arthroplasty for acute fracture. *J Bone Joint Surg Am*. 2004;86-A(9):1983-8.

17. Costain DJ, Whitehouse SL, Pratt NL, Graves SE, Ryan P, Crawford RW. Perioperative mortality after hemiarthroplasty related to fixation method. A study based on the Australian Orthopaedic Association National Joint Replacement Registry. *Acta Orthopaedica* 2011;82(3):275-281.

18. Jameson SS, Khan SK, Baker P, James P, Gray A, Reed MR, Deehan DJ. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. *QJM*. 2012;105(5):455-60.

19. O'Reilly RF, Burgess IA, Zicat B. The prevalence of venous thromboembolism after hip and knee replacement surgery. *MJA*. 2005;182:154-159.

20. Oger E, Bressollette L, Nonent M, Lacut K, Guias B, Couturaud F, Leroyer C, Mottier D. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. *Thromb Haemost*. 2002;88:592-7.

21. Petersen MB, Jørgensen HL, Hansen K, Duus BR. Factors affecting postoperative mortality of patients with displaced femoral neck fracture. *Injury*. 2006;37(8):705-11.

22. Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, Kim K, Meeks T, Kraemer HC. A new brief instrument for assessing decisional capacity for clinical research. *Arch Gen Psychiatry*. 2007 Aug;64(8):966-74.

APPENDIX A

Additional Details Pertaining to Study Design for Clinical Trials

Appendix A must be completed for investigator/student initiated research projects that require review by the convened board. For example, studies that use investigational test articles, that present more than minimal risk to subjects, or that involve prisoners, must be reviewed by the convened board.

Note that for studies requiring review by the convened board the full board application must be completed, data safety monitoring must be addressed (e.g. by completion of Appendix B to the main application) and the Investigator Brochure and /or package insert must also be submitted if available.

1. *For a clinical trial (e.g. a Phase I, II or III study), the use of the intervention must be fully described e.g., the treatment regimen for use of drugs, placebo, medical device etc. Also include plans for receipt of test article, storage, dispensing and reconciliation*. : The intervention, the application of either 1 gram of tranexamic acid mixed with normal saline (0.9% NaCl) for a total volume of 50 cc or 50 cc of normal saline (0.9% NaCl) placebo, will occur intra-operatively just prior to wound closure. One half, or 25 cc, of either the study drug or the saline placebo will be applied intra-articularly. The second half, or 25 cc, will be applied under the fascia. When applying either the study drug or saline placebo, the resident performing the case or the attending surgeon will attempt to coat all exposed tissues with a thin layer of the aqueous solution. This is a one-time dose. Provision of the study drug (Tranexamic acid or saline placebo) will be provided by the hospital pharmacy. The pharmacy is responsible for the storing and dispensing the study drug.

2. *Provide a description of known adverse events due to the intervention and the plan to deal with such adverse events (e.g. does reduction, removal of device, removal from trial.):* The package insert for Tranexamic acid provides a section on known adverse reactions with injection of the drug. Gastrointestinal disturbances (nausea, vomiting, diarrhea), allergic dermatitis, giddiness, and hypotension have been reported occasionally with intravenous injection. Worldwide post marketing reports include thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) have been rarely reported. Convulsion, chromatopsia, and visual impairment have also been reported. However, due to the spontaneous nature of reporting of medical events and lack of controls the actual incidence and causal relationship of the drug and event cannot be determined.

   There is no information regarding adverse reactions with topical use of tranexamic acid in the package insert. A review of the literature revealed a Cochrane review on topical application of tranexamic acid for the reduction of bleeding. Ker et al. reported topical use of the drug was not

associated with an increased rate of complications. Topical use of the drug was associated with a relative risk of 0.28 (95% CI, 0.06-1.34; P = 0.11) for mortality, 0.33 (95% CI, 0.04-3.08; P = 0.33) for myocardial infarction, 0.33 (95% CI, 0.01-7.96; P = 0.49) for stroke, 0.69 (95% CI, 0.31-1.57; P = 0.38) for DVT, and 0.52 (95% CI, 0.09-3.15; P = 0.48) for pulmonary embolism [6]. These rates were comprised from 29 randomized control trials with 2,612 patients.

In the event an adverse event occurs, the surgeon and patient will be un-blinded and the patient will be treated according to standard medical practices. Adverse events will include mortality and thromboembolic events (pulmonary embolism, deep vein thrombosis, myocardial infarction, cerebrovascular accident, acute renal cortical necrosis, central retinal artery or vein obstruction).

3. *Describe circumstances that may lead to a subject being removed from the trial by the PI, e.g. due to failure to follow study procedures, and the process for doing so*: Since the study involves a one time intra-operative dose of tranexamic acid or placebo, there is no specific study procedure that the patient will be required to follow. Patients will be removed from the trial if the assigned intervention is not available to the operating room staff prior to wound closure.

4. *Describe any stopping rules for the study:* The study will be stopped if an increase in the rate of mortality, pulmonary embolism, deep vein thrombosis, myocardial infarction, cerebrovascular accident, acute renal cortical necrosis, or central retinal artery or vein obstruction is observed. These are considered to be rare events following elective hip hemiarthroplasty. The study stopping rules for these events are described in the following table:

Adverse Event	Stopping Criteria	Reference(s)
Mortality	The 30-day mortality rate following hip hemiarthroplasty has been reported to range from 2.4% to 10.1%. Assuming a conservative estimate of 6.25% mortality and a sample size of 102 patients, we would expect to see 6-7 patient deaths overall during our study period,	*The 30-day mortality rate in patients undergoing hip arthroplasty for displaced hip fracture was 2.4% (186 of 7774).* Parvizi J, Ereth MH, Lewallen DG. Thirty-day mortality following hip

	which begins on the date of surgery and ends 4-6 weeks postoperatively. In each 51 patient subgroup, we would expect to see 3-4 patient deaths over the study period when applying this 6.25% mortality rate. If death occurs in 5 patients in the tranexamic acid subgroup (1 death above the expected), the study will be stopped and an inter-group assessment will occur (see below). If 4 or fewer patient deaths (3 to 4 patient deaths are expected based upon our conservative assessment of the literature) occur in the tranexamic acid subgroup, the study will be continued until completion. It is possible that the placebo group will have a higher number of deaths due to chance, due to our conservative estimate of mortality rate (6.25%) for our study duration, or due to a protective effect from tranexamic acid. Mortality rates following hip hemiarthroplasty are variable. Topical use of tranexamic acid has been associated with a relative risk of 0.28 (95% CI, 0.06 to 1.34; P = 0.11) for mortality. If the placebo group has experienced a greater number of deaths than would be expected from our conservative estimate based upon the available literature (n = 5 or greater), we will continue the study. If 5 patient deaths (1 above the expected) occur in the tranexamic acid subgroup and 4 or fewer patient deaths have occurred in the placebo subgroup, the study will be stopped. If 5 patient deaths (1 above the expected) occur in the tranexamic acid subgroup and 5 or more deaths have already occurred in the placebo subgroup, we will continue the study. In this instance, the study will either continue to completion or be stopped if at any point the number of deaths in the tranexamic subgroup exceeds that of the control.	arthroplasty for acute fracture. J Bone Joint Surg Am. 2004 Sep;86-A(9):1983-8. *At one month, 359 out of 3,634 (9.9%) patients receiving a cemented hemiarthroplasty and 1,051 out of 10,362 (10.1%) patients receiving a cementless hemiarthroplasty had died.* Costain DJ, Whitehouse SL, Pratt NL, Graves SE, Ryan P, Crawford RW. Perioperative mortality after hemiarthroplasty related to fixation method. A study based on the Australian Orthopaedic Association National Joint Replacement Registry. Acta Orthopaedica 2011;82(3):275-281. *The 90-day mortality rate of patients undergoing hip hemiarthroplasty was 9.8% in patients 65-84 years of age and 18.3% in patients $\geq$ 85 years of age* Jameson SS, Khan SK, Baker P, James P, Gray A, Reed MR, Deehan DJ. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. QJM. 2012 May;105(5):455-60. *Topical use of the tranexamic acid is associated with relative risk of 0.28 (95% CI, 0.06 to 1.34; P = 0.11) for mortality.* Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 7.
Pulmonary Embolism	A 1.2% rate of in-hospital pulmonary embolism has been reported for patients undergoing total hip arthroplasty. A rate of	*The number of patients who experienced a symptomatic in-hospital pulmonary embolism in*

	1.1% to 1.3% has been reported at 90 days for patients who underwent hip hemiarthroplasty. Assuming a conservative estimate of 1% for the rate pulmonary embolism in this patient population, we expect to see 0-1 patients develop a pulmonary embolism in the tranexamic acid subgroup (n = 51). The occurrence of pulmonary embolism in 2 patients (1 above the expected) in the tranexamic acid subgroup will be sufficient to stop the study for an inter-group assessment. As with mortality, it is possible that the placebo subgroup will have a higher incidence of pulmonary embolism. If 2 patients (1 above the expected) in the tranexamic acid subgroup experience a pulmonary embolism and if 2 or more patients in the placebo group have already experienced a pulmonary embolism, we will continue the study. In this instance, the study will continue to completion or be stopped if at any point the number of patients with a pulmonary embolism in the tranexamic acid subgroup exceeds that of the control. If 2 patients in the tranexamic acid subgroup experience a pulmonary embolism and 1 or fewer patients in the placebo subgroup have experienced a pulmonary embolism, the study will be stopped.	*patients undergoing total hip replacement was 37/3028 (1.2%).* O'Reilly RF, Burgess IA, Zicat B. The prevalence of venous thromboembolism after hip and knee replacement surgery. MJA. 2005; 182: 154-159. *The 90-day incidence of pulmonary embolism in patients undergoing hip hemiarthroplasty was 1.3% (540/41,770) in patients 65-84 years old and 1.2% (422/35,321) in patients 85 years or older.* Jameson SS, Khan SK, Baker P, James P, Gray A, Reed MR, Deehan DJ. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. QJM. 2012 May;105(5):455-60.
Deep Vein Thrombosis (DVT)	Deep vein thrombosis is a complication following surgery that is highly dependent upon screening practices. When asymptomatic patients admitted to the hospital have been indiscriminately screened with ultrasound, deep vein thrombosis rates have ranged from 5.5% to 17.8%. Following total hip arthroplasty, a deep vein thrombosis rate of 8.9% has been reported in patients within 7 days postoperatively with universal screening. Treatment for deep vein thrombosis involves a protracted course of pharmacologic anticoagulation, which is associated with	*The prevalence of asymptomatic deep vein thrombosis on admission was 5.5% and reached 17.8% in patients above 80 years of age.* Oger E, Bressollette L, Nonent M, Lacut K, Guias B, Couturaud F, Leroyer C, Mottier D. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. Thromb Haemost. 2002; 88: 592-7. *The number of patients developing*

	potentially lethal bleeding complications. Therefore, current standards of care require screening in symptomatic patients only, to prevent diagnosing and treating asymptomatic individuals with clinically insignificant DVTs. Though screening is limited to symptomatic individuals, the threshold for initiating screening amongst clinicians is variable. The decision to initiate screening is also susceptible to detection bias. The rates of deep vein thrombosis following hip hemiarthroplasty have been reported to range from 1.1% to 1.3%. Since this diagnosis is so dependent upon variable screening practices and since we believe study inclusion may result in a lower clinical threshold for screening, we will assume a rate of 3% as a conservative estimate of the deep vein thrombosis rate in this patient population. Assuming a conservative estimate of 3% for the rate of deep vein thrombosis in this patient population, we expect to see 1-2 patients develop a deep vein thrombosis in the tranexamic acid (n = 51) subgroup. The occurrence of deep vein thrombosis in 3 patients (1 above the expected) in the tranexamic acid subgroup will be sufficient to stop the study for inter-group assessment. As with mortality, it is possible that the placebo subgroup will have a higher incidence of deep vein thrombosis. If 3 patients (1 above the expected) in the tranexamic acid subgroup experience a deep vein thrombosis and if 3 or more patients in the placebo group have experienced a deep vein thrombosis, we will continue the study. In this instance, the study will continue to completion or be stopped if at any point the number of patients with a deep vein thrombosis in the tranexamic acid subgroup exceeds that of the control. If 3 patients in the tranexamic acid subgroup experience a deep vein thrombosis and 2 or	*deep vein thrombosis within 7 days postoperatively was 263/3028 (8.9%) after total hip replacement.* O'Reilly RF, Burgess IA, Zicat B. The prevalence of venous thromboembolism after hip and knee replacement surgery. MJA. 2005; 182: 154-159. *The 90-day incidence of deep vein thrombosis in patients undergoing hip hemiarthroplasty was 1.3% (537/41,770) in patients 65-84 years old and 1.1% (383/35,321) in patients 85 years or older.* Jameson SS, Khan SK, Baker P, James P, Gray A, Reed MR, Deehan DJ. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. QJM. 2012 May;105(5):455-60.

	fewer patients in the placebo subgroup have experienced a deep vein thrombosis, the study will be stopped.	
Myocardial Infarction	The 30-day incidence of myocardial infarction following hip hemiarthroplasty has been reported to be 1.9% in patients 65-84 years of age (790 in 41,770 patients) and 3.1% in patients $\geq$ 85 years of age (1101 in 35,321 patients). Assuming a rate of 1.9% to 3.1% for myocardial infarction in this patient population, we would expect to see 1-2 patients in the tranexamic acid subgroup (n = 51) experience a myocardial infarction in the 4-6 week period following the surgical intervention. The occurrence of myocardial infarction in 3 patients (1 above the expected) in the tranexamic acid subgroup will be sufficient to stop the study for inter-group assessment. As with mortality, it is possible that the placebo subgroup will have a higher incidence of myocardial infarction. If 3 patients (1 above the expected) in the tranexamic acid subgroup experience a myocardial infarction and if 3 or more patients in the placebo subgroup have experienced a myocardial infarction, we will continue the study. In this instance, the study will either continue to completion or be stopped if at any point the number of myocardial infarction in the tranexamic subgroup exceeds that of the control. If 3 patients (1 above the expected) in the tranexamic acid subgroup experience a myocardial infarction and fewer than 3 patients in the placebo subgroup have experienced a myocardial infarction, the study will be stopped.	*The 30 day incidence of myocardial infarction is 1.9% in patients 65-84 years of age and 3.1% in patients $\geq$ 85 years of age.* Jameson SS, Khan SK, Baker P, James P, Gray A, Reed MR, Deehan DJ. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. QJM. 2012 May;105(5):455-60.
Cerebrovascular Accident	The 30-day incidence of cerebrovascular accident following hip hemiarthroplasty has been reported to range from 0.1% to 1.5%.	*The 30 day incidence of stroke is 0.1% in patients 65-84 years of age and 0.1% in patients $\geq$ 85 years of*

(Stroke)	Assuming an anticipated rate of 0.1% to 1.5%, we would expect 0-1 patients in the tranexamic acid subgroup (n = 51) to experience a cerebrovascular accident in the 4-6 week period following their surgical intervention. The occurrence of cerebrovascular accident in 2 patients in the tranexamic acid subgroup (1 event above the expected) will be sufficient to stop the study for an inter-group assessment. As with mortality, it is possible that the placebo subgroup will have a higher incidence of cerebrovascular accident. If 2 patients (1 above the expected) in the tranexamic acid subgroup experience a cerebrovascular accident and if 2 or more patients in the placebo subgroup have experienced a cerebrovascular accident, we will continue the study. In this instance, the study will either continue to completion or be stopped if at any point the number of patients with a cerebrovascular accident in the tranexamic subgroup exceeds that of the control. If 2 patients (1 above the expected) in the tranexamic acid subgroup experience a cerebrovascular accident and fewer than 2 patients in the placebo subgroup have experienced a cerebrovascular accident, the study will be stopped.	*age.* Jameson SS, Khan SK, Baker P, James P, Gray A, Reed MR, Deehan DJ. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. QJM. 2012 May;105(5):455-60. *The rate of stroke after hip hemiarthroplasty has been reported to be 0.9% for men and 1.5% for women.* Petersen MB, Jørgensen HL, Hansen K, Duus BR. Factors affecting postoperative mortality of patients with displaced femoral neck fracture. Injury. 2006 Aug;37(8):705-11.
Acute Renal Cortical Necrosis	There is no literature regarding the prevalence of acute renal cortical necrosis following hip hemiarthroplasty. Acute renal cortical necrosis is mentioned as an adverse event that has been spontaneously noted in post-marketing analysis of intravenous use of tranexamic acid. The occurrence of 1 episode of acute renal cortical necrosis in the tranexamic acid subgroup (n = 51) will be sufficient to stop the study for inter-group assessment. If 1 patient (1 above the expected) in the tranexamic acid subgroup experiences acute renal cortical necrosis and if 1 or more patients in the placebo subgroup have experienced acute renal	

	cortical necrosis, we will continue the study. In this instance, the study will either continue to completion or be stopped if at any point the number of acute renal cortical necrosis in the tranexamic subgroup exceeds that of the control. If 1 patient (1 above the expected) in the tranexamic acid subgroup experiences acute renal cortical necrosis and no patients in the placebo subgroup have experienced acute renal cortical necrosis, the study will be stopped.	
Central Retinal Artery/Vein Obstruction	There is no literature regarding the prevalence of central retinal artery or vein obstruction following hip hemiarthroplasty. Central retinal artery or vein obstruction is mentioned as an adverse event that has been spontaneously noted in post-marketing analysis of intravenous use of tranexamic acid. The occurrence of 1 episode of central retinal artery or vein obstruction in the tranexamic acid subgroup (n = 51) will be sufficient to stop the study for inter-group assessment. If 1 patient (1 above the expected) in the tranexamic acid subgroup experiences a central retinal artery or vein obstruction and if 1 or more patients in the placebo group have experienced a central retinal artery or vein obstruction, we will continue the study. In this instance, the study will either continue to completion or be stopped if at any point the number of central retinal artery or vein obstructions in the tranexamic acid subgroup exceeds that of the control. If 1 patient (1 above the expected) in the tranexamic acid subgroup experiences a central retinal artery or vein obstruction and no patients in the placebo subgroup have experienced a central retinal artery or vein obstruction, the study will be stopped.	

5. *Additional Comments by PI:* The stopping rules were developed based on the available literature regarding complication rates following hip hemiarthroplasty. While rare, complications including death occur in this population following hip hemiarthroplasty. Additionally, these rates vary from study to study. In developing the stopping criteria we used the conservative estimates of adverse events in an effort to prevent overestimating the true rate of occurrence. Using these estimates we considered both the number needed in the tranexamic group to constitute stopping the study as well as the relative difference between the study groups. Given the heterogeneous nature of the patient population and the variability between institutions reporting these events, we may observe a larger number of occurrences in adverse events in both groups. To account for this potential increase in rates across the entire study cohort, the stopping criteria includes comparisons of the number of events between the two groups. Un-blinded data will be reviewed by an independent data safety monitoring board.