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Katherine Balzano-Cowan
University of New England

Morgan Guerrette
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Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures

Katherine Balzano-Cowan, SRNA and Morgan Guerrette, SRNA

University of New England

Advisors: Maribeth Massie, Ph.D. (c), MS, CRNA and John Hanlon, DNP, MSNA, CRNA
Minimizing perioperative blood loss during orthopedic surgery has proven challenging for providers. Perioperative utilization of antifibrinolytic pharmacologic interventions, such as tranexamic acid (TXA), has been demonstrated as a safe and effective technique for decreasing blood loss and allogenic blood transfusion rates. Currently, the Food and Drug Administration (FDA) approved on-label indications of TXA are for use in short-term treatment of hemophilia patients undergoing dental extractions and in management of patients experiencing menorrhagia (Mayeux, Alwon, Collins, & Hewer, 2016). Despite the current limited scope of FDA approval for TXA, use in elective surgery with otherwise clotting-uncompromised patients is not a new concept. Perioperative TXA administration in elective joint replacement surgery, cardiopulmonary bypass, spinal fusions, and hysterectomies has been well studied (Duncan et al., 2015). Numerous studies have acknowledged TXA use decreases perioperative blood loss, decreases perioperative blood transfusions, and shortens length of hospital stay. Additionally, research exists that demonstrates safety and efficacy of TXA use in patients presenting with traumatic injury (Roberts et al., 2013). Despite this vast body of knowledge, little research exists evaluating TXA use in hip fractures. Over 325,000 traumatic hip fractures occur every year (Neuman, Rosenbaum, Ludwig, Zubizarreta, & Silber, 2014). This patient population is generally frail and typically lacks optimization prior to urgent surgery. Based on the extensive body of prior research conducted to date, it is reasonable to postulate that TXA use in these instances would yield a decreased blood loss and therefore contribute to lower rates of allogenic blood transfusion in hip fracture patients.
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Introduction

Finding new and innovative methodologies to reduce surgical blood loss is a major area of interest among orthopedic surgeons. Over the past two decades a variety of techniques ranging from blood salvage systems to pharmacologic approaches have been examined as means to accomplish this goal and reduce the number of allogenic blood transfusions required during and after orthopedic surgical procedures. In recent years, employment of pharmacologic methods has become increasingly popular. Specifically, administration of an antifibrinolytic agent during the perioperative period has been proven to be an effective means of decreasing intraoperative bleeding. The reduction of intraoperative bleeding is expected to confer a benefit to the patient by reducing the need for allogenic blood and blood product transfusions as well as the sequale associated with such transfusions (Das, Vijay, Bedi, & Mitra, 2013). One antifibrinolytic in particular, tranexamic acid (TXA), has been well studied for use in scheduled, elective orthopedic surgery with heavy emphasis on total hip arthroplasty (THA) and total knee arthroplasty (TKA) (Charoencholvanchanich & Siritwattanasakul, 2011). TXA is a lysine amino acid derivative that prevents break down of the fibrin clot. TXA competitively binds to plasminogen. This competitive binding action obstructs naturally occurring lysine from binding with plasminogen thus preventing the formation of the enzyme plasmin. Inhibition of the conversion of plasminogen to plasmin preserves the formed fibrin clot thereby decreasing blood loss at the site of bleeding or injury via clot stabilization (Vijay, Bedi, Mitra, & Das, 2013).

Despite the over 325,000 hip fractures currently occurring each year in the United States and with hip fracture rates projected to increase each year reaching an estimated 500,000 per year in 2040 (Neuman, Rosenbaum, Ludwig, Zubizarreta, & Silber, 2014), research examining
the efficacy of utilizing TXA in hip fracture surgery is quite limited. Recent studies have generally been conducted on a relatively smaller scale and been limited to scheduled, elective procedures. The focus of these studies has centered primarily on the ability of TXA administration to reduce overall blood loss, examination of the incidence of adverse thrombolic vascular occlusive events associated with the administration of TXA, or both. In supplementation to these findings, The CRASH-2 Trial: A Randomized Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion Requirement in Bleeding Trauma Patients (CRASH-2) study by Roberts et al. (2013), reviewed later in this paper, provides high quality evidence suggestive of both the safety and efficacy of TXA use in patients presenting with traumatically sustained injuries and otherwise normal coagulation profiles.

While there is substantial high quality evidence supporting both the safety and efficacy of TXA use to reduce overall blood loss and need for allogenic blood transfusions during both scheduled orthopedic joint procedures as well as traumas, a limited quantity of research exists in support of administration of TXA to traumatic hip fracture patients (Roberts et al., 2013). These patients are not optimized for surgery and are therefore considered fragile and potentially more vulnerable during the postoperative period. Administration of an antifibrinolytic agent to reduce blood loss in patients who have sustained traumatic hip injuries has the potential to greatly improve patient outcomes.

This lack of high quality peer reviewed evidence prompted the organization of such a research study to be conducted at Central Maine Medical Center (CMMC). Central Maine Medical Center is located at 300 Main Street in Lewiston, Maine. The hospital serves most of Androscoggin County, Maine and various small and medium-sized communities (Central Maine
Medical Center, n.d.). CMMC is a 300-bed, Level-II trauma center which preforms over 9,000 surgeries annually (Central Maine Medical Center, n.d.). CMMC is a teaching affiliate of Boston University School of Medicine as well as University of New England College of Osteopathic Medicine (Central Maine Medical Center, n.d.).

Currently, a research proposal (please see Appendix A for the entire proposal) has been created, submitted to, and approved by the IRB at CMMC (please see Appendix E for approval letter). This paper will examine the literature reviewed to construct the proposal, an outline of the study methods and goals, as well as a progress update. All materials generated for submission to the IRB, IRB applications, patient handouts, informed consent literature, and approval documentation are attached in the appendices of this paper (Appendix B, C, and D).

**Literature Review**

TXA is a lysine amino acid derivative that aids in the prevention of the break down of existing clots. TXA competitively binds to plasminogen preventing the formation of the enzyme plasmin. By blocking the conversion of plasminogen to plasmin, the fibrin clot is stabilized and continues to exist thus decreasing the amount of blood lost at the site of injury or surgical incision (Napolitano, Cohen, Cotton, Schreiber, & Moore, 2013). Currently, TXA is only approved by the US Food and Drug Administration (FDA) in oral short term use for patients with hemophilia needing dental surgery and for the treatment of menorrhagia (Mayeux, Alwon, Collins, & Hewer, 2016). However, antifibrinolytics are actively being used off label in multiple types of surgery including cardiopulmonary bypass, elective total joint replacements, ear, nose, and throat (ENT), and spinal fusions.

Because TXA disrupts the normal process of clot dissolution, safety questions around its use regarding a potential increase in the incidence of thromboembolic events have emerged.
Consideration of patient safety is of paramount concern when proposing or initiating research on human subjects. Initial research results examined discussed the potential for increased adverse vascular occlusive events that may be associated with TXA administration to patients with an intact clotting profile. The largest of these studies was The CRASH-2 Trial: A Randomized Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion Requirement in Bleeding Trauma Patients (CRASH-2) study conducted by Roberts et al. (2013). This level I evidence, multicenter, randomized, placebo-controlled study examined the administration of TXA to “adult trauma patients with or at significant risk for bleeding and were within eight hours of injury undergoing surgical intervention to address their injuries and/or cause of bleeding” (Roberts et al., 2013, p. 1). In this study 10,096 adult trauma patients were administered a one gram loading dose of TXA over 10 minutes and started on an infusion of one gram of TXA over eight hours within eight hours of sustaining their traumatic injury. For control comparison, 10,115 patients were administered normal saline in the same manner. As previously stated, CRASH-2 is one of the largest studies conducted to date examining the potential effects of TXA administration. CRASH-2 assessed the use of TXA in trauma patients with the goal of reducing death rates due to uncontrolled bleeding. Results from CRASH-2 showed a significant decrease in bleeding following trauma and ultimately determined that the administration of TXA to trauma patients yielded a decrease in the observed death rate. The mortality rate observed in the TXA group was 4.8% compared to 6.1% in the placebo group. Additionally, CRASH-2 revealed that TXA safely decreased the risk of death without increasing the risk of vascular events. The rate of a vascular occlusion, such as a myocardial infarction, deep vein thrombosis, or pulmonary embolism, was 1.7% for patients that received TXA and 2% for those who received the placebo (Roberts et al, 2013).
Ultimately, this study concluded that administration of TXA within three hours of initial injury “safely reduced the risk of death in bleeding trauma patients and (TXA) is highly cost-effective” (Roberts et al., 2013, p. 1). Furthermore, CRASH-2 helped establish TXA as an essential medication on the World Health Organization’s (WHO) list. The WHO list of essential medications declares certain medications should be available in ample amounts at affordable pricing due to their proven safety and efficacy as demonstrated by use with positive outcomes on a large number of patients (Roberts et al., 2013).

Duncan et al. (2015) conducted a single center retrospective cohort study demonstrating the safety of TXA administration to patients with normal coagulation profiles. Individual orthopedic surgeons within the institution had been using TXA on a patient-by-patient basis when they determined a potential benefit was present. The orthopedic department on the whole came to the conclusion TXA offered a benefit to the majority of the patients undergoing joint surgeries. A protocol for its routine use was established. The institution sought positive affirmation that TXA was a safe and effective means to reduce bleeding during scheduled orthopedic procedures and approved the study proposed by Duncan et al. (2015). Patients included in this study were undergoing either an elective THA or TKA. Patient data over a 5-year period was collected, collated, and examined to determine if administration of TXA contributed to an increased incidence of untoward vascular occlusive events. Duncan et al. (2015) concluded “the overall frequency of clinically significant (venous thromboembolism) VTE was lower when TXA was administered, and the odds of postoperative VTE were unchanged” (Duncan et al., 2015, p. 275). As additional positive support to the primary study finding, the authors noted “no statistically significant change was seen in 30-day mortality,
although a trend toward reduced mortality with TXA administration was observed” (Duncan et al., 2015, p. 275).

Having found evidence in support of the safety of TXA use in both scheduled as well as trauma surgeries, the search expanded to examine current evidence attesting to the efficacy of perioperative TXA administration. One such study consisted of a large meta-analysis looking at amicar, tranexamic acid, and aprotinin (Zufferey et al., 2006). No significant increase in thromboembolic events stemming from the use of these three antifibrinolytic therapies was found during this study. These results serve to corroborate the safety of administration of antifibrinolytic agents during surgical procedures reported by other studies. Additionally, all three antifibrinolytics showed a decrease in the amount of surgical blood loss and there was a concomitant decrease in the rate of allogenic blood transfusions required in the postoperative period. Zufferey et al. (2006) found that aprotinin and tranexamic acid specifically decrease blood loss and blood transfusion rates when administered during the perioperative period in orthopedic surgery.

Vijay, Bedi, Mitra and Das (2013) examined the ability of TXA to reduce perioperative blood loss during scheduled orthopedic procedures. They focused their study solely on the use of TXA in patients undergoing hip fracture surgery. Patients were either a physical classification status I or II between the ages of 18 and 80. Of the 90 participants in this study, 45 were randomized into the test group and received TXA while 45 were randomized into the control group and did not receive TXA. Primary outcomes for this study included examination of the volume of blood in the patients surgical site drain postoperatively, percentage of hemoglobin fall on postoperative day zero and day two, and allogenic blood transfusion rates. The blood volume output into the surgical site drains for the TXA group was 39.33 +/- 10.09 mL compared to 91.11
+/- 17.61 mL in the control group. Hemoglobin drop in the TXA on day zero was 2.99 +/- 3.45 mL compared to the control group of 7.70 +/- 6.05 mL. On postoperative day two, TXA hemoglobin drop was 0.35 +/- 0.74 g/dL and the control group was 2.72 +/- 2.7 g/dL. Eighteen of the 45 patients in the control group received an allogenic blood transfusion while only seven out of 45 patients in the TXA group required transfusion (Vijay et al., 2013). The level I evidence presented by Vijay et al. (2013) demonstrated the ability of TXA administration in the perioperative period to be an effective means to reduce postoperative blood loss and realize a reduced transfusion requirement for patients during major hip surgeries.

In a 2011 Cochrane Review, the safety and efficacy of TXA was addressed (Henry et al., 2011). A placebo was compared to TXA when examining the rate of allogenic blood transfusions and adverse vascular events. A total of 4,842 patients were randomized into either the placebo/control group or the TXA group. Patients who received TXA saw a reduction in the rate of allogenic blood transfusions by 39%. There was no increased risk of patients experiencing a thromboembolic event including stroke, deep vein thrombosis, myocardial infarction, pulmonary embolism, or development of renal disease reported in this study. Henry et al. (2011) also showed there was no correlation between an increase in mortality and the use of TXA.

Pongcharoen and Ruetiwarangkoon (2015) made conclusions similar to Duncan et al. (2015). In their paper, a prospective controlled study was performed to examine the total amount of surgical blood loss experienced as well as the incidences of adverse vascular occlusive events experienced by their study participants. Patients in this study were followed for a minimum of 12 months in an effort to determine if the potential for delayed untoward vascular events existed. While patients in the TXA group of this study were found to have experienced lower amounts of
intraoperative blood loss, this result was not statistically significantly. More germane to the context of the research being conducted at Central Maine Medical Center, this level I evidence study demonstrated that patients in both the TXA group as well as the control group “did not present the clinical signs of (deep venous thrombosis) DVT and (pulmonary embolism) PE. They also did not show other thromboembolic events including cerebral vascular accidents or myocardial infarctions” (Pongcharoen & Ruetiwarangkoon, 2016, p. 7). This study continues to support the safety profile of TXA use in patients with uncompromised coagulation profiles.

Numerous level I, II, and one level III quality of evidence studies have examined the concomitant reduction of blood loss and safety of TXA administration to patients undergoing orthopedic procedures. Poeran et al. (2014) conducted a retrospective cohort study of 510 hospitals in the United States looking at patients undergoing elective TKA or THA. Patients were grouped into those who received TXA in any form or dose versus those that did not. Poeran et al. (2014) found that TXA was an effective pharmacological intervention for the reduction in the need for allogenic blood transfusions while it did not produce an increased risk for adverse vascular complications in patients receiving the drug.

Hart et al. (2014) examined the incidence of transfusion rates for over 23,000 patients that received either a total knee arthroplasty or a total hip arthroplasty. Patients in this study did not receive an antifibrinolytic agent of any kind. Allogenic blood transfusion rates were found to be as high as 22% for total hip arthroplasty and 18.3% for total knee arthroplasty (Hart et al., 2014). Transfusion rates were deemed high given the number of patients in this study. Additionally, Hart et al. (2014) determined the mortality rate was increased in those patients who did receive a transfusion. Due in part to these findings as well as countless others like it,
administration of TXA in elective joint replacement surgery has now become routine due to the high incidence of allogenic transfusion rates.

In a randomized, double blind study involving 99 patients timing of TXA administration in total knee arthroplasty patients was examined (Tanaka et al., 2001). Tanaka et al. (2001) sought to determine the time for TXA administration that would achieve the greatest reduction in blood loss. They determined that administration prior to incision and again once the tourniquet was deflated showed the greatest reduction in perioperative blood loss. Regardless of the timing of administration, Tanaka et al. (2001) indicated there was a 40% decrease in blood loss after the administration of TXA. Additionally, there was no reported increase in thromboembolic events observed during this study. These findings once again support the safety as well as the efficacy of TXA administration.

Blood loss continues from the time of injury throughout the perioperative period. Blood oozes from the ends of cut bone, open intra-medullary canals, and from soft tissue after dissection (Sepah et al., 2011). Over a three-year period patients undergoing a total knee arthroplasty were randomized into two groups: those who received TXA or those who received a placebo. Postoperatively, recipients of TXA experienced a mean blood loss from their drain of 826-1,288 mLs whereas the placebo group experienced drainage of 1,828-2,695 mLs. Once again, these findings present evidence that advocates for the use of TXA to decrease patient blood loss during the perioperative period. None of the patients in the Sepah et al. (2011) study experienced problematic vascular events from the use of TXA. This finding is supportive of the safety of TXA.

One of the major motivating factors behind seeking methods to control perioperative blood loss is the potential need for patients experiencing high levels of surgical blood loss to
require allogenic blood transfusions during the perioperative period. Zhang, Chen, Chen, and Que (2011) conducted a systematic literature review study examining 15 randomized control studies encompassing 842 patient outcomes. Zhang et al. (2012) determined that administration of TXA during the perioperative period reduced the total blood loss and reported that the risk of transfusion was reduced by 56% due to the administration of TXA. Further, the use of TXA did not yield an increase in the risk of deep vein thrombosis when administered to patients with an intact clotting profile undergoing TKA (Zhang et al., 2012). Other similar studies also considered the benefit of giving TXA to reduce perioperative bleeding during TKA and THA to determine if a reduction in the number of perioperative allogenic blood product transfusion could be achieved with positive outcomes. One retrospective quality of care chart review comparison of data before vs. after implementation of a TXA administration protocol found that data collected supported the perioperative administration of TXA due to its ability to reduce the number of blood transfusions required while not increasing the number of observed adverse vascular events (Baker et al., 2015). Baker et al. (2015) reported that as the utilization of TXA increased from 45.8% to 95.3% in patients undergoing TKA the rate of allogenic transfusions required in patients during the postoperative period was reduced from 8.8% to 5.2%. While findings presented by Baker et al. (2015) is level III evidence, Gandhi, Evans, Mahomed, & Mahomed (2013) presented level I evidence in support of utilization of TXA in the perioperative period to realize a reduction in the number of postoperative allogenic blood transfusions. Patients undergoing both THA as well as TKA were included in this Cochrane Review by Gandhi et al. (2013). Specific interventions were very similar; all patients in the study test groups were intravenously administered TXA in either variable doses ranging from 10-15 mg/kg or 500-1,500 mg fixed doses prior to incision (Gandhi et al., 2013). Gandhi et al. (2013)
demonstrated that the number of patients receiving allogenic transfusions was less in the TXA groups when compared to the control groups. Additionally, there was no increase in the number of patients developing deep vein thrombosis or other untoward thromboembolic complications in the TXA groups as compared to the control groups. This study, once again, offered high quality evidence supporting both the safety and efficacy of TXA in addition to its ability to realize a statistically significant reduction in the number of allogenic blood product transfusions required to be given to patients undergoing scheduled orthopedic joint procedures.

Lee, Freeman, Edmondson, & Rogers (2015) examined 305 patients who underwent a total hip arthroplasty. In this study, the efficacy of TXA administration to decrease perioperative blood loss and allogenic blood transfusions was examined. Lee et al. (2015) reported data on over 300 patients who received a total hip arthroplasty and were randomized into either those who received TXA or the control group who did not receive TXA. It was found that those who received TXA experienced a lower transfusion rate. Transfusion rates were 6% in patients that received TXA and 19% in patients that did not receive TXA. Hemoglobin was also measured preoperatively and postoperatively in these patients. Postoperative hemoglobin dropped by 26% in the patients that received TXA and 42% in the non-TXA control group. The patients that received TXA exhibited a large reduction in both transfusion rates and overall drop in hemoglobin level. Henry et al. (2015) estimated that the use of TXA prevents one blood transfusion per every eight patients, thus supporting the routine use of TXA in orthopedic surgery.

Charoencholvanich and Siritractanakul (2011) examined the duration of action of TXA. They sought information about its ability to help decrease blood loss and blood transfusion rates in the postoperative period. Therapeutic levels of TXA were detected in peripheral blood
samples for up to eight hours following administration. This coincides with the duration of hyperfibrinolysis that can last up to eight hours following any kind of injury or trauma. Hyperfibrinolysis is an increased state of clot dissolution following disruption of normal homeostasis. Homeostasis is disrupted as soon as injury occurs or surgical incision occurs. Additionally, 65% of blood drainage happens in the first eight hours following surgery.

Charoencholvanich and Siriwattanosakul (2011) randomized 100 patients undergoing a total knee arthroplasty into two groups. One group received a placebo and the second group received a bolus of TXA. Both groups received standard treatment prior to incision and again after deflation of the tourniquet. Postoperative drainage was estimated to be 1,208mLs +/- 421mLs in the placebo group and 727mLs +/- 234mLs in the group that received TXA. The number of patients requiring an allogenic blood transfusion was decreased by 56-90% with the administration of TXA (Charoencholvanich & Siriwattanosakul, 2011). These findings again support the use of TXA in orthopedic surgery to aid in decreasing the requirement for blood product transfusions.

Administration of TXA is also being used in joint revision surgery, as these procedures tend to have a greater blood loss due to increased manipulation during removal of the existing hardware. After mobilization and removal of old hardware, new hardware then needs to be placed, increasing the potential blood loss. Samujh, Falls, Wessel, Smith, & Malikani (2014) examined TXA administration solely in total knee arthroplasty revisions. Their research found a clinically significant decrease in allogenic blood transfusion rates in the patient group receiving TXA. The control group in this study, as a whole, used 25 units of blood whereas the TXA group required the use of only three units of blood. Also the transfusion rate reported in the control group was 30.3% compared to 16.7% in the TXA receiving group. This clinically
significant observed decrease in blood transfusion rate again supports the perioperative administration of TXA. Untoward vascular events were documented in this study. Thromboembolic events occurred in 3% of patients from the control group (2 out of 68 patients) and 2% (1 out of 43 patients) of patients in the TXA group (Samujh et al, 2014). While an unfortunate occurrence contributing to overall morbidity, the incidence of vascular events reported was higher in the control group versus the TXA group suggesting it was not the administration of TXA that contributed to the reported events.

**Review of Dosing Strategies**

Having found significant amounts of high quality evidence within the current body of literature to support the safety of administration of TXA to patients, as well as extensive literature to support the use of TXA as a means to reduce overall perioperative blood loss, the dosing strategy for the proposed study required determination of an appropriate evidence based schedule and amount of drug to be administered. George, Sarraf, & Nwaboku (2015) examined the effect of TXA dose timing on the perioperative total blood loss as well the rate of allogenic blood transfusion and incidence of thromboembolic complications. Secondarily, the cost of utilizing the drug was also considered. While this study also focused on primary THA and TKA, the underlying safety information as well as their findings related to the timing of the administration of TXA are what was most relevant to the proposed study at Central Maine Medical Center. Patients in the George, Sarraf, & Nwaboku (2015) study “who received TXA showed a reduction in immediate postoperative red cell volume loss and total blood loss” (George, et al., 2015, p. 129). Because of this finding, the primary conclusion of this study was that “a single perioperative bolus of intravenous TXA may significantly reduce operative blood loss” (George et al., 2015, p. 129) in a cost-conscious manner. Additionally, George et al.
(2015) cited the successful use of TXA in the CRASH-2 study on trauma patients to reduce bleeding and also went on to discuss the large body of scientific publications that “have confirmed the efficacy of TXA in significantly reducing operative blood loss and reducing the need for postoperative blood replacement” (George et al., 2015, p. 129).

Similar to George et al. (2015), Sarzaeem et al. (2014) also examined a variety of dosing schedules and manners of administration of TXA in an effort to reduce perioperative blood loss. Sarzaeem et al. (2014) conducted a level I evidence study including patients 18 years of age and older undergoing unilateral TKA due to degenerative arthritis of the knee. Unlike other studies, patients in this study were not excluded due to prior cardiovascular issues, cerebrovascular conditions or a history of thromboembolic disorders. Patients in this study were allocated to groups using a random number list system. Groups were labeled 1-4. Group 1 received 1,500mg of TXA via intravenous injection just prior to incision. Group 2 had the joint undergoing replacement irrigated with three grams of TXA dissolved into 100mL of normal saline. Group 3 had 1,500mg of TXA injected into the drain port after surgical closure had been achieved. Group 4 was the control group and had no TXA of any kind administered. Sarzaeem et al. (2014) found that the administration of TXA by any method does indeed reduce bleeding as evidenced by a reduction in the overall level of hemoglobin decrease. The intravenous injection of TXA appeared to be considerably more efficacious than the irrigation of the joint or wound drainage port, and that all groups did realize a reduction in bleeding when compared to the control group (Sarzaeem et al., 2014).

Gomez-Barrena, Ortega-Andreu, Padilla-Eguiluz, Perez-Chrzanowska & Figueredo-Zalve (2014) examined the difference between topical intra-articular TXA and intravenous TXA in reducing blood loss during total knee arthroplasty. Results showed the two routes of
administration to be equally efficacious in regard to the amount of total blood loss and blood drainage postoperatively. TXA levels were measured in the peripheral blood postoperatively. When peripheral blood levels of TXA were taken during the postoperative period, the intra-articular group exhibited a TXA level significantly lower than what was observed in the intravenous TXA group. Administration of topical TXA gave the same results as intravenous TXA administration in terms of decreasing blood loss and drained blood. However, topical administration of TXA significantly reduces the risk of thromboembolic occurrence by decreasing systemic circulation of TXA (Gomez-Barrena et al., 2014).

According to Meyeux et al. (2016), when TXA is used to reduce blood transfusion rates, large institutional cost savings can be realized and potentially passed along to patients. The cost of one unit of packed red blood cells to the patient is $343 compared to $45-55 for one gram of TXA. Additionally, blood products may be limited in their availability making administration of TXA even more desirable. Routine TXA administration, unless contraindicated, has the potential to drastically improve resource allocation. Administration of TXA decreases the cost to the patient and also serves to reduce the morbidity and mortality that is a potential result from blood product administration (Meyeux et al., 2016).

Contraindications to receiving TXA have been put into two categories: absolute contraindications and relative contraindications (Meyeux et al., 2016). Color blindness, hypersensitivity to TXA, active intravascular clotting and subarachnoid hemorrhage are considered absolute contraindications. Evaluation for TXA toxicity is performed through an eye exam. The ophthalmic exam is only useful to detect TXA toxicity in patients who have functioning color vision. In patients who are color blind, providers are not able to distinguish if TXA toxicity exists and must therefore not be administered TXA (Meyeux et al., 2016).
of a vascular occlusive event, administration of a procoagulant therapy, or hormonal contraceptive use is considered to be relative contraindications for the use of TXA (Meyeux et al., 2016).

Blood loss in hip fractures starts at the time of injury and continues throughout the perioperative period. Foss (2006) concluded that total intraoperative blood loss from a hip fracture is up to six times the amount observed. Hidden blood loss of 547-1,473 mLs contributes to patient complications postoperatively. Large blood loss during surgery in a vulnerable elderly population drastically increases medical complications and increased length of hospital stay (Foss, 2006).

Shokoohi et al. (2012) examined the effects of hip fracture surgery and blood transfusions on the elderly population. Shokoohi et al. (2012) concluded that blood transfusions did not confer an increase in mortality but was associated with an increase in postoperative infections following hip fracture surgery. Mortality was measured at postoperative day 28 and 180. No difference in transfused versus non-transfused patients was reported. Bleeding is associated with any type of fracture however in this specific postoperative population, even small amounts of blood loss put these patients at risk for hypovolemia and anemia. Transfused patients also have an increase in length of hospital stay when compared to those patients who did not receive transfusions (Shokoohi et al, 2012). Shokoohi et al. (2012) serves as support for utilizing TXA as a means of decreasing transfusion rates in the frail elderly population experiencing hip fractures as an effort to reduce infection rates and decrease length of hospital stay.

Zufferey et al. (2010) studied the use of TXA in hip fracture surgery as a means to reduce blood loss. One hundred and ten patients participated in the study. Patients received one dose of TXA prior to incision and a second dose three hours later. The rate of allogenic blood
transfusion was 42% in the TXA group as compared to 60% in the control group (Zufferey et al., 2010). A slightly increased incidence of adverse vascular events reported in this study however, this increase was not statistically significant (Zufferey et al., 2010).

Discussion: Study at Central Maine Medical Center

The number of hip fracture occurrences in the United States is increasing every year, with the majority of hip fractures happening in a vulnerable elderly patient population. Hip fracture in this population is associated with a mortality rate of 7-14% while still in the hospital and reaches 14-36% within a year of surgery (Mundi, Pindiprolu, Simunovic, & Bhandari, 2014). An increased risk of death is associated with a hip fracture and persists for up to six years post injury (Yonezawa, Yamazaki, Atsumi, & Obara, 2009). Factors contributing to the risk of death within six years of fracture are: preoperative health status, pre-fracture mobility, age, sex and comorbidities (Yonezawa et al, 2009). Common comorbidities in this population are dementia, congestive heart failure, coronary heart disease, previous myocardial infarction, renal failure, chronic lung disease, and diabetes (Neuman, Rosenbaum, Ludwig, Zubizarreta, & Silber, 2014). Mortality after hip fracture is linked to a decrease in postoperative mobility that is associated with a simultaneous decline in overall health status and quality of life (Mundi et al, 2014). Up to half of all hip fracture patients do not regain their pre-fracture functionality. Additionally, 20% of hip fracture patients require some form of long-term care due to the inability to preform activities of daily living and decreased mobility (Tajeu et al., 2013).

For the nine-month period ending on September 30th, 2016, CMMC is experiencing a 19% transfusion rate for patients undergoing surgical repair of hip fractures in their facility. This compares to a 1.5% transfusion rate for primary elective hip replacement surgeries where TXA is being administered prophylactically during the perioperative period. As discussed above in the
literature review presented, administration of antifibrinolytic therapy during the perioperative period has been offered as a means to decrease intraoperative bleeding. The reduction in intraoperative bleeding is assumed to confer a benefit to the patient by reducing the need for infusion of and sequale associated with allogenic blood and blood product transfusions. The primary objective of the CMMC study is to determin if the use of TXA reduces perioperative blood loss and therefore reduces the need for allogenic blood transfusion in patients undergoing surgery to repair hip fracture. Secondary objectives of this study will examine calculated blood loss between the TXA and placebo groups, determination if the reduction in allogenic blood transfusion imparts a parallel reduction in the incidence of complications such as infection, length of hospital stay, and death. Additionally, we seek to determine if use of TXA in this patient population imparts an increased risk of adverse vascular events and/or death. Should data indicate any such increased risk, the study will be terminated prior to scheduled completion and all current study participants will be notified.

To take part in this prospective, randomized, double-blinded, off label trial study at CMMC, patients are required to meet certain inclusion criteria. Patients must be greater than 65 years of age. Patients must present with an acute, traumatic hip fracture sustained after a fall from standing. Patients who acquired their hip fractures after high impact collisions are excluded from participation. Patients must freely provide their informed consent. Additionally, patients meeting inclusion criteria for this study must be without history of treatment with anticoagulation agents, vascular events such as stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, or a clotting disorder. Patients presenting with an unknown medical history, or if a full medical history cannot be obtained, may not be included in the study.
Patients may be enrolled into the study by one of the study’s Clinical Research Coordinators. The Principal Investigator, Co-Principal Investigator, Sub-Investigators, or Clinical Research Coordinators are able to obtain informed consent from prospective patients or their legal representative. When patients enter the facility with a hip fracture via the Emergency Department, the registered nurse (RN) House Supervisor will alert the Clinical Coordinator to their arrival. This will trigger the Clinical Coordinator to review the patient’s history and physical, demographics, and nature of their injury. Should the patient meet the inclusion criteria, outlined in the above paragraph, the Clinical Research Coordinator may approach the patient to consent them for enrollment into the study. Once informed consent has been obtained, a Clinical Research Coordinator will then personally deliver the consent to the pharmacy where the consent will be secured in a locked filing cabinet. Sarah Green, PharmD will be unblinded in this study. She will produce randomized kits in the CMMC Inpatient Pharmacy numbered from one to 125. Randomized TXA and placebo kits will be created in batches of 20. Half of the kits will contain TXA and half will contain placebo. As patients are added to the study, the Inpatient Pharmacy will dispense the kits based on the patient’s number of entry into the study. When a patient is enrolled into the study by a Clinical Research Coordinator, they will be sequentially added to the study list and tracked by FIN number within the Inpatient Pharmacy by Sarah Green. No personal identifier will be used in the randomization. No one participating in the study, patient or provider, will have access to identifying information enabling him or her to determine which patients are receiving active drug vs. placebo. Thus meeting the definition of calling a study double blinded. Participants in the placebo group will be administered 100 mL of normal saline 15 minutes prior to skin incision. Participants in the intervention group will be administered
1,000 mg tranexamic acid reconstituted into 100 mL of normal saline 15 minutes prior to skin incision.  

A wide variety of dosages and timing regimes for a single perioperative dose of TXA were examined throughout the literature search and review. The findings presented by George et al. (2015) were utilized to determine the most efficacious timing for the dose of TXA to be administered to the traumatic hip population being examined in the CMMC study. George et al. (2015) determined a single 1,000 mg dose of TXA would confer the previously reported benefit of reduced bleeding. This is a simplified and conservative dosing schedule that has been shown to reduce bleeding and was therefore chosen due to both its simplicity as well as its demonstrated efficacy.  

In the postoperative period all patients will have vital signs and hemoglobin and hematocrit levels monitored per institutional standards of care. Vital signs will be checked every four hours and laboratory values will be checked daily, or more frequently at individual provider discretion. Patients meeting institutional requirements for a blood transfusion during either the intraoperative or postoperative period will be considered for the primary outcome. As stated in our hypothesis in Appendix A: IRB Application, we expect the pre-incision administration of TXA will reduce the rate of intraoperative and postoperative allogenic blood transfusion.  

The patient’s independent medical team on the institution’s Hospitalist service will determine the need for and if criteria are met for blood transfusion. CMMC protocol requires patients meet certain requirements prior to receiving allogenic red blood cell transfusion. In the setting of active bleeding institutional requirements for red blood cell transfusion include: acute blood loss of >25% of blood volume unresponsive to fluid resuscitation, acute blood loss with a hemoglobin of <9g/dL with moderate to severe cardiovascular disease, or a decrease in
hemoglobin level of 2g/dL within 24 hours with a hemoglobin of less than 8g/dL or hematocrit less than 24g/dL with signs or symptoms of anemia. Signs or symptoms of anemia are defined as fatigue, pallor, shortness of breath, lightheadedness, heart rate >100 beats per minute, and lab values revealing hemoglobin and hematocrit levels less than 9g/dL and 24g/dL respectively. As previously stated, an independent medical team will follow patients who require transfusion of blood products. Patients will receive post transfusion evaluation of hemoglobin and hematocrit levels at time intervals determined to be medically necessary by the hospitalist or surgeon responsible for their care. Typically, patients will receive daily checks of hemoglobin and hematocrit level until they are able to maintain a stable hemoglobin level >7g/dL and hematocrit level >21g/dL in the absence of the signs or symptoms of anemia previously described.

Patients participating in this study will be allowed to ambulate in the same manner as all other orthopedic surgical patients. Postoperative weight bearing will be allowed as tolerated. DVT prophylaxis will follow standard hospital procedure. Patients will receive 5,000 units of subcutaneous heparin on admission and every eight hours thereafter until 12 hours prior to surgery. Six hours post surgical intervention, patients will resume heparin therapy. Additionally, when patients are not participating in physical rehabilitation activities, sequential calf compression devices shall also be utilized to further reduce the risk of developing DVT.

Determination of blood loss will be calculated in the manner described below.

- Estimated blood volume (EBV) preop: weight in kg * average blood volume mL/kg
  - Adult men: 75mL/kg
  - Adult women: 65 mL/kg
- Multiplying the estimated blood volume by the hematocrit gives the red cell volume.
• Performing the calculation preoperatively and postoperatively then computing the difference calculates pre-operative vs. post-operative changes in red cell volume.
  o Pre-op RBC volume = EBV * pre-op Hct
  o Post-op RBC volume = EBV * post-op Hct
  o Operative RBC volume loss = Pre-op RBC volume – Post-op RBC volume

Infection at the site will be characterized and reported per institution protocol. Adverse vascular events that may be considered include myocardial infarction as diagnosed by a cardiologist based on ECG changes, elevated biological markers (creatine kinase, troponin), or echocardiogram changes and symptomatic DVT verified by ultrasound venography, pulmonary embolism confirmed by CT scan of the chest, pulmonary angiography, echo-cardiologic visualization or visualization of thrombus at autopsy.

This study has been approved by the IRB at Central Maine Medical Center to run for one years time with a goal N=125. Should the number of patients enrolled for outcome examination fail to be achieved in the approved timeframe, application for extensions will be considered on a yearly basis by the IRB. To date, there have been 12 patients enrolled into the study. Data will be collected and examined on a quarterly basis. The first gathering of raw data is to occur at the end of March 2017. Given the considerably lower than expected number of patients willing and able to be enrolled into the ongoing study, the Central Maine Medical Center research team is currently reexamining the schedule for data collection and review. Currently, deliberation continues regarding what would represent the most efficient and productive time schedule to convene and assess data collected to date.
Conclusion

A multitude of recent and high quality studies that have been conducted validate the efficacy and safety of TXA administration. A wide range of patient populations presenting with varied surgical needs were examined within each of these research studies. Results have shown that without question, use of TXA during a variety of scheduled orthopedic procedures has been revealed as an effective means to decrease blood loss during the perioperative surgical period (Zufferey et al. 2006). The reduction of intraoperative bleeding is assumed to confer a benefit to the patient by reducing the need for infusion of, and sequelae associated with, allogenic blood and blood product transfusions (Das et al. 2013). However, a significant gap in current literature exists. Very few recent high-quality studies examine administration of TXA to hip fracture patients. Of those, Zufferey et al. (2010) is perhaps the most germane to the study currently being conducted at Central Maine Medical Center. Zufferey et al. (2010) examined the rates of allogenic blood transfusion after two doses of TXA, as discussed above in the literature review section of this paper. This study utilized a small number of patients, N=100, and showed a non-statistically significant increase in the number of adverse vascular events. The limitations of the Zufferey et al. (2010) study were its small size, limited duration, and inability to determine with any statistical importance if an increase in adverse vascular occlusive events can be seen when administering TXA to patients undergoing surgery for correction of a traumatic hip fracture. The study underway at CMMC plans to address these two shortcomings of the previously conducted study by Zufferey et al. (2010).

The ongoing study being conducted out of Central Maine Medical Center aims to provide high-quality evidence to support the use of TXA in the traumatic hip fracture population. This will be done by increasing the number of patients examined from the N=100 cases considered by
Zufferey et al. (2010) to N=125. The increase in sample size will increase the power of any hypothesis testing done at the completion of the study. The duration of the study is currently approved for one year however, may be easily extended with submission of a renewal application to the CMMC IRB. Given the expedited approval received after submission of the initial application, it is expected renewal and extension will not be an issue. The CMMC study utilizes a single dose of TXA and is expected to improve overall patient outcome through the reduction of blood loss while concomitantly maintaining a low level of vascular sequale that may be attributed to the use of an antifibrinolytic therapy in the setting of trauma.

Numerous studies, as discussed in detail above, support the use of TXA in elective joint replacement surgery to decrease perioperative blood loss. Some of these studies also demonstrate that TXA administration decreases blood transfusion rates, length of hospital stay, and cost to the patient. Patients undergoing elective orthopedic surgery have been medically optimized to achieve the most successful outcomes. Patients who have sustained a traumatic hip fracture may not be optimized and are therefore more likely to be considered fragile given their age, trauma status, preoperative baseline health, and presence of perioperative blood loss. When considering these factors, decreasing blood loss during the perioperative period and reducing the need for allogenic transfusion is likely to realize improved postoperative outcomes in this patient population.


Vijay, B. S., Bedi, V., Mitra, S., & Das, B. (2013). Role of tranexamic acid in reducing postoperative blood loss and transfusion requirement in patients undergoing hip and


Appendix A

IRB Application

Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures

List of Abbreviations:

TXA: Tranexamic Acid  
CMMC: Central Maine Medical Center  
DVT: Deep Vein Thrombosis  
LOS: Length of Stay  
ENT: Ear Nose and Throat

Principal Investigator, Research Team, and Study Site:

Principal investigator: Morgan Guerrette  
Co-Principal Investigator: Katherine Balzano-Cowan  
Clinical Research Coordinators: Tina Moring, Sarah Green, James Osgood, Elizabeth Turcotte, Jay Bachelder, Robyn Begin, Carie Whitmore, Maija Comeau, and Diane Jeselskis  
Study site: Central Maine Medical Center

Study Information:

Study Title: Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures  
Study Population: Any patient greater than 65 years of age presenting with traumatic hip fracture  
Study Design  
Sample Size: n=125  
Study Duration: 1 year  
Study Agent: Tranexamic acid

Primary Objective: Determination if the use of TXA reduces perioperative blood loss and therefore reduces the need for allogenic blood transfusion in patients undergoing surgery to repair hip fracture.

Secondary Objectives:  
Secondary objectives of this study will examine calculated blood loss between the TXA and placebo groups, determination if the reduction in allogenic blood transfusion imparts a concomitant reduction in the incidence of complications such as infection (defined below), LOS, and death. Additionally, we seek to determine if use of TXA in this patient population imparts an increased risk of adverse vascular events (defined below) and death.
**Intervention Description:** Study participants will be assigned to either the placebo group or the intervention group. Participants in the placebo group will be administered 100mL of normal saline 15 minutes prior to skin incision. Participants in the intervention group will be administered 1,000mg tranexamic acid reconstituted into 100mL of normal saline 15 minutes prior to skin incision.

All patients will have vital signs and hemoglobin and hematocrit levels monitored per institutional standards of care. Patients meeting institutional requirements for a blood transfusion (see below) during either the intraoperative or postoperative period will be considered for the primary outcome. We expect the pre-incision administration of TXA will reduce the rate of intraoperative and postoperative allogenic blood transfusion.

The patient’s independent medical team will determine the need for and if criteria are met for blood transfusion. CMMC protocol requires patients meet the following requirements prior to receiving allogenic red blood cell transfusion:

In the setting of active bleeding a patient must have:

1. Acute blood loss of >25% of blood volume unresponsive to fluid resuscitation  
   Or
2. Acute blood loss with a hemoglobin of <9 with moderate to severe cardiovascular disease  
   Or
3. A decrease in hemoglobin level of 2gm/dL within 24h with a hemoglobin of less than 8/hematocrit less than 24 with signs or symptoms of anemia

An independent medical team will follow patients receiving transfusion of blood products. Patients will receive post transfusion evaluation of hemoglobin and hematocrit levels at time intervals determined to be medically necessary by the hospitalist or surgeon responsible for their care. Typically, patients will receive daily checks of hemoglobin and hematocrit level until they are able to maintain a stable hemoglobin level >7 and hematocrit level >21 in the absence of signs or symptoms of anemia.

Patients participating in this study will be allowed to ambulate in the same manner as all other orthopedic surgical patients. Postoperative weight bearing will be allowed as tolerated. DVT prophylaxis will follow standard hospital procedure. Patients will receive 5,000 units of subcutaneous heparin on admission and every 8 hours thereafter until 12 hours prior to surgery. 6 hours post surgical intervention patients will resume heparin therapy. Additionally, when patients are not participating in physical rehabilitation activities sequential calf compression devices shall also be utilized to further reduce the risk of developing DVT.

Blood loss will be calculated using the following:

- Estimated blood volume (EBV) preop: weight in kg * average blood volume mL/kg  
  - Adult men: 75mL/kg  
  - Adult women: 65 mL/kg
- Multiplying the estimated blood volume by Hct gives the red cell volume
TRANEXAMIC ACID AND HIP FRACTURES

- Performing the calculation preoperatively and postoperatively then computing the difference calculates pre-op vs. post-op changes in red cell volume.
  - Pre-op RBC volume = EBV * pre-op Hct
  - Post-op RBC volume = EBV * post-op Hct
  - Operative RBC volume loss = Pre-op RBC volume – Post-op RBC volume

Infection at the site will be characterized per institution protocol.

Adverse vascular events may be considered:
- Myocardial infarction as diagnosed by a cardiologist based on ECG changes, elevated biological markers (CK, troponin), or echocardiogram changes.
- Symptomatic DVT verified by ultrasound venography, pulmonary embolism confirmed by CT scan of the chest, pulmonary angiography, echo-cardiologic visualization or visualization of thrombus at autopsy.

**Background and Significance:**

As of Q3 2016, CMMC is experiencing a 19% transfusion rate for patients undergoing surgical repair of hip fractures in our facility. This compares to a 1.5% transfusion rate for primary elective hip replacement surgeries where TXA is being administered prophylactically during the perioperative period.

Administration of antifibrinolytic therapy during the perioperative period has been presented as a means to decrease intraoperative bleeding. The reduction in intraoperative bleeding is assumed to confer a benefit to the patient by reducing the need for infusion of and sequelae associated with allogenic blood and blood product transfusions (5,16). One antifibrinolytic in particular, tranexamic acid (TXA), has been well studied for use in scheduled elective orthopedic surgery with emphasis on total hip arthroplasty and total knee arthroplasty (1, 6, 8, 11). TXA is a lysine amino acid derivative that prevents break down of the fibrin clot. TXA competitively binds to plasminogen. This competitive binding action obstructs naturally occurring lysine from binding with plasminogen thus preventing the formation of the enzyme plasmin. Inhibition of the conversion of plasminogen to plasmin preserves the formed fibrin clot thereby decreasing blood loss at the site of bleeding or injury via clot stabilization (2, 8, 9,).

CRASH-2 (27) is one of the largest studies to date conducted for the purpose of examining the effects of TXA administration. CRASH-2 assessed the use of TXA in trauma patients with the goal of reducing death rates due to uncontrolled bleeding. Results from CRASH-2 showed a significant decrease in bleeding following trauma and ultimately determined that the administration of TXA to trauma patients yielded a decrease in the observed death rate (27). Due to the promising results observed in the CRASH-2 study, The World Health Organization (WHO) was prompted to add TXA to its list of essential medications for trauma and those at significant risk of ongoing hemorrhage (2, 10).

Currently, the FDA approved on-label indications of TXA are use in the short-term treatment of hemophilia patients undergoing dental extractions and in the management of patients
experiencing menorrhagia (10). Despite the current limited scope of FDA approval for TXA, antifibrinolytic therapy use during elective surgery in otherwise clotting-uncompromised patients is not a new concept. TXA has been administered in cardiopulmonary bypass, ENT, orthopedic, spinal fusions, and hysterectomies as an aid to decrease blood loss. Numerous studies have examined the efficacy, and safety, of TXA use for the reduction of intraoperative blood loss in orthopedic surgeries specifically, total knee and total hip arthroplasty (21). In reports examining lower total joint replacement surgeries, TXA reduced intraoperative blood loss, rate of allogenic blood transfusions, and total length of hospital stay (18,19,20,22). All of these individual results appear to work synergistically and ultimately resulted in a reduction in the overall cost of the procedure and decreased costs relayed to the patients (8, 11,16). Limited research exists examining the efficacy of TXA administration in the perioperative period for the traumatic hip fracture population. Based on the entire body of prior research conducted to date, it is reasonable to hypothesize that administration of TXA in these traumatic instances would also yield a decreased blood loss and therefore could possibly contribute to lower rates of allogenic blood transfusion in the traumatic hip fracture population.

Each year over 300,000 hip fractures occur in the United States. This number is projected to increase to over 500,000 by the year 2040 (23, 25). In the >65-year-old population, one-year mortality rate associated with hip fracture is between 12% to 36% in the 65 and older population and the 5-year mortality rate reaches upwards of 60% (24, 25). Factors affecting mortality include pre-existing comorbid conditions, preoperative health status, pre-fracture mobility, age, and sex (9). With blood loss beginning at the moment of injury and continuing through out the postoperative recovery period, typical patients may experience an average perioperative blood loss in upwards of 1500 mLs (28,12). Significant blood loss in an already vulnerable elderly population has the potential to dramatically increase the need for allogenic blood transfusions. Allogenic blood transfusions have been linked to an increase in postoperative infection rates and prolonged hospital stays (3,11). Patients that receive allogenic blood transfusions are twice as likely to develop an infection when compared to non-transfused patient cohorts (3).

Cardiac disease and renal disease are common comorbid conditions exhibited by a majority of the elderly hip fracture patient population (9). Patients with significant cardiac disease have an increased incidence of poor outcomes in the presence of large volume blood loss. Patients with pre-existing renal compromise are at risk for pulmonary complications associated with volume loading during receipt of allogenic blood transfusion. Reduction of allogenic blood transfusions in both the renal and cardiac compromised hip fracture population has the potential to significantly decrease the risk of known adverse events frequently seen in patients with these pre-existing comorbid conditions.

Lee et al (29) examined the efficacy of TXA administration in patients receiving hip hemiarthroplasty surgery following a hip fracture. Transfusion rates within the TXA group were reported at 6% and for those in the placebo group at 19%. Zuffrey et al (7) explored the use of antifibrinolytics in orthopedic surgery to reduce allogenic blood transfusions. Three antifibrinolytic were used in this study: aprotinin, amicar and TXA. For the purpose of this study only results pertinent to TXA will be discussed. Primary surgeries investigated included total knee arthroplasty and total hip arthropalasty. Allogenic blood transfusion rates and the total periooperative blood loss were significantly (P<0.01) decreased when TXA was administered.
Zuffrey et al (7) also examined complications in the setting of antifibrinolytic administration. The rate of venous thromboembolism in the TXA group (20.9%) was no different when compared to the control group (20.8%).

In a second study by Zufferey et al (15) the use of TXA in hip fracture surgery was studied. One hundred and ten patients participated in the study. Patients received one dose of TXA prior to incision and a second dose 3 hours later. The rate of allogenic blood transfusion was 42% in the TXA group as compared to 60% in the control group. A slightly increased incidence of adverse vascular events reported in this study was not statistically significant (15).

Poren et al (13) investigated the safety of TXA use in 872,416 patients undergoing total hip arthroplasty and total knee arthroplasty. The primary outcome of this study was TXA use to decrease allogenic blood transfusions while not increasing the risk for thromboembolic complications. Patients that received TXA exhibited an allogenic transfusion rate of 7.7% while the control group had at 20.1% transfusion rate. Thromboembolic complications occurred at a rate 0.6% in the TXA group as compared to 0.8% in the control group. Poren et al demonstrated the ability of TXA to decrease the requirement of allogenic blood transfusions while not significantly increasing adverse vascular outcomes.

Das et al (14) focused their study solely on the use of TXA in patients undergoing hip fracture surgery. Patients were either an ASA (American Society of Anesthesiologist) physical classification status I or II between the ages of 18-80. Of the 90 participants in this study, 45 were randomized into the test group and received TXA while 45 were randomized into the control group and did not receive TXA. Primary outcomes for this study included examination of the volume of blood in the patients surgical site drain postoperatively, percentage of hemoglobin fall on postoperative day 0 and day 2, and allogenic blood transfusion rates. The blood volume output into the surgical site drains for the TXA group was 39.33+/-10.09ml compared to 91.11+/-17.61 in the control group. Hemoglobin drop in the TXA on day 0 was 2.99+/-3.45 compared to the control group of 7.70+/-6.05. On postoperative day 2, TXA hemoglobin drop was 0.35+/-0.74 and the control group was 2.72+/-2.7. Eighteen of the 45 patients in the control group received an allogenic blood transfusion while only 7 out of 45 patients in the TXA group required transfusion.

A 2011 Cochran Review (30) examined the effect of using TXA vs. placebo on the rate of allogenic blood transfusion and adverse vascular events. A total of 4,842 patients were randomized into either the TXA group or the control group receiving a placebo. The population receiving TXA realized a reduction in the rate of allogenic blood product transfusion of 39%. Furthermore, the risk of adverse vascular events such as myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, or development of renal disease or dysfunction did not increase when TXA was administered. Also, the use of TXA was not associated with an increase in risk for mortality (30).

Literature review has shown that limited evidence exists looking at the efficacy of TXA use for decreasing allogenic blood transfusion in hip fracture patients. This study aims to provide high quality evidence to support the use of TXA in the traumatic hip fracture population. Use of a single dose of TXA is expected to improve overall patient outcome through the reduction of
blood loss while concomitantly maintaining a low level of vascular sequale that may be attributed to the use of an antifibrinolytic therapy in the setting of trauma.

Numerous studies support the use of TXA in elective joint replacement surgery to decrease perioperative blood loss, decrease blood transfusion rates, decrease length of hospital stay, and decrease cost to the patient. Patients undergoing elective orthopedic surgery have been medically optimized to achieve the most successful outcomes. Patients who have sustained a traumatic hip fracture may not be optimized and are therefore more likely to be considered fragile given their age, trauma status, preoperative baseline health, and presence of perioperative blood loss. When considering these factors, decreasing blood loss during the perioperative period and reducing the need for allogenic transfusion is likely to realize improved postoperative outcomes in this patient population.

**Objectives:**

**Primary Objective:** Determine if the use of TXA reduces perioperative blood loss and therefore reduces the need for allogenic blood transfusion in patients undergoing surgery to repair hip fracture.

**Secondary Objectives:** Determine if the reduction in allogenic blood transfusion imparts a concomitant reduction in the incidence of complications such as infection, LOS, and death. Determine if use of TXA in this patient population imparts an increased risk of adverse vascular events and death.

**Study design/methodology:**
This is a prospective, randomized, double-blinded, off label trial. Any patient at or over the age of 65 presenting to CMMC for the ORIF repair of a traumatic hip fracture may be considered for inclusion in this study.

Patients may be enrolled into the study by one of the study’s Clinical Research Coordinators. The Clinical Research Coordinators able to obtain informed consent are the M2 Clinical Coordinators Jay Bachelder, Robyn Begin, Carie Whitmore, or Maija Comeau. When patients enter the facility with a hip fracture via the Emergency Department, the RN House Supervisor will alert the M2 Clinical Coordinator to their arrival. This will trigger the Clinical Coordinator to review the patient’s history and physical, demographics, and nature of their injury. Should the patient meet the inclusion criteria outlined below, the Clinical Research Coordinator may approach the patient to consent them for enrollment into the study. Informed Consent will be obtained by reading the Informed Consent literature to the patient and answering any questions that may arise. The Clinical Research Coordinator will then personally deliver the consent to the pharmacy where the consent will be secured in a locked filing cabinet.

**Study Population:**
**Inclusion/Exclusion Criteria:**

**Inclusion Criteria:** Any patient over the age of 50 presenting to Central Maine Medical Center with hip fracture that consents to participate in the study may be included in the study.
**Exclusion Criteria:** Patients who are anticoagulated or have a history of vascular events such as stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis or a clotting disorder. Patients with unknown medical histories or if a full medical history can not be obtained they will be excluded from the study.

**Study Drug/Interventions:**
Study participants will be randomly assigned to either the placebo group or the intervention group. Participants in the placebo group will be administered 100mL of normal saline 15 minutes prior to skin incision. Participants in the intervention group will be administered 1,000mg tranexamic acid reconstituted into 100mL of normal saline 15 minutes prior to skin incision.

Sarah Green, PharmD will be unblinded in this study. She will produce randomized kits in the CMMC Inpatient Pharmacy numbered from 1 to 125. Randomized TXA and placebo kits will be created in batches of 20. ½ of the kits will contain TXA and ½ will contain placebo. As patients are added to the study, the Inpatient Pharmacy will dispense the kits based on the patient’s number of entry into the study. When a patient is enrolled into the study by one of the Clinical Research Coordinators, they will be sequentially added to the study list and tracked by FIN number within the Inpatient Pharmacy by Sarah Green. No personal identifier will be used in the randomization.

**Study Schedule:**
The study will take place starting 01/11/2017 to 01/11/2018

**Adverse Event Reporting:**
Adverse events are entered into the MIDAS system at CMMC. Either the RN or provider responsible for direct patient care may make entries into the MIDAS system. All adverse events related to orthopedic patients involved in this study will be reported to Elizabeth Tourcotte.

**Statistical Analysis Plan:**
N=125
Defer to statistician.

**Informed Consent Process:**

**Privacy and confidentiality**
Privacy and confidentiality will be maintained pursuant to hospital policy and standards.

Patients or their healthcare decision makers will be verbally consented by their surgeon prior to enrollment in the study. Signed consent forms will be obtained as verification. Additionally, an informational handout detailing the study objectives as well as potential risks and benefits to participation will be provided to patients at the time of consent.

**Risk/Benefit:**

**Risk to participants:**
Adverse vascular event including, but not limited to, myocardial infarction, symptomatic DVT, pulmonary embolism are possible. Zuffery et al (15) reported the probability of vascular events at 6 weeks post receipt of TXA was 16% vs. 6% in their placebo group while a larger study conducted by Das et al (14) reported no thromboembolic episodes. It was suggested that TXA will not affect the risk of DVT due to its mechanism of action whereby TXA inhibits fibrinolysis in the wound but not in circulation.

Medications that have been shown to have an interaction with IV TXA:

- Anti-inhibitor Coagulant Complex (Examples: Autoplex T, Feiba NF, Feiba VH Immuno): Antifibrinolytic Agents may enhance the thrombogenic effect of Anti-inhibitor Coagulant Complex. Combination should be avoided
- Contraceptives-Estrogens and Progestin (Examples: Yaz, Desogen, brevicon) May enhance the thrombogenic effect of Tranexamic Acid. R
- Fibrinogen Concentrate (Examples: haemocomplettan, fibrinogene T1 and Clottagen): Antifibrinolytic Agents may enhance the adverse/toxic effect of antifibrinolytic agents. Specifically, the risk for thrombosis may be increased.
- Tretinoin (Examples: Avita, Renova, Retin-a): May enhance the thrombogenic effect of Antifibrinolytic Agents.

Benefits to participants:
Reduction in blood loss after experiencing a traumatic hip fracture. The additional benefits stemming from a reduction in blood loss are the reduction in the need to receive blood products. Allogenic blood product transfusion carries with it some level of risk which is outlined in other areas of this research proposal in more detail.

Study Timeline:
1 year

Data Safety Monitoring:
CMMC currently utilizes the MIDAS system for reporting and follow-up on any adverse patient events. Elizabeth Turcotte will be notified directly through the MIDAS reporting system of any adverse event occurrence as described above. Elizabeth Turcotte will present any adverse events reported during monthly data reporting meetings with the group at large. Informed consent is only for use in enrolling patients into the TXA study and not used as a consent for surgical intervention. The TXA study consents will be secured in pharmacy in a filing cabinet that is locked at all times, it is not to become part of the patients’ chart. The coordinators will take the consents and bring to the pharmacy to then be secured.

Conflict of Interest:
None

Publication and Presentation Plans:
Morgan and Kate will be using this as capstone project and presenting at UNE Research day.

References:


Appendix B

Central Maine Healthcare Corporation
INSTITUTIONAL REVIEW BOARD
Central Maine Medical Center
Bridgton Hospital
Rumford Hospital

Deborah Taylor, Ph.D., IRB Chair
Jenae Limoges, MD, IRB Vice-chair
Phone: (207) 795-8246
Fax: (207) 344-0373

APPLICATION (FULL BOARD)

<table>
<thead>
<tr>
<th>Protocol Title:</th>
<th>Principal Investigator:</th>
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<tr>
<td>Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures</td>
<td>Morgan Guerrette SRNA</td>
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Application for Human Subject Research
Applications for human subject research will need to meet all outlined requirements listed for each type of review in order for a project to be reviewed. If you have any questions regarding how to complete the forms or need help locating a form, please call our office at 207-795-8246.

Authority of the IRB and IRB Review
The IRB determines if a project meets the federal definition of research: “a systematic investigation including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” The IRB defines a human subject as: “a living individual about whom an investigator conducting research obtains: 1) data through intervention or interaction with the individual, or 2) identifiable private information.” This determination is made with the aid of the OHRP guidance document: Human Subject Regulations Decision Charts, dated September 24, 2004.

Types of IRB Review
There are three levels of IRB Review (full board, expedited and exempt), determined by the nature of the project, level of potential risk to human subjects and the subject population.

Exempt and expedited review can be given to studies that constitute no more than minimal risk to the human subjects, i.e., the risk one experiences in daily living. These reviews are done in the IRB office on a continual basis.

Full board review is required for studies that involve greater than minimal risk or vulnerable populations that require special protections by the IRB. These require review by the convened IRB.

Research Proposals Involving the Use of Protected Health Information (PHI)
How Can Covered Entities Use and Disclose Protected Health Information for Research and Comply with the Privacy Rule?

Key Points:

- De-identified health information, as described in the Privacy Rule, is not PHI, and thus is not protected by the Privacy Rule. (See List of Identifiers)

- PHI may be used and disclosed for research with an individual's written permission in the form of an Authorization.
• PHI may be used and disclosed for research without an Authorization in limited circumstances:
  Under a waiver of the Authorization requirement, as a limited data set with a data use agreement,
  preparatory to research, and for research on decedents’ information.

### Submission and Review Procedure for Full Board Review

The IRB will provide written notification of the IRB’s determination within ten (10) business days. This
notification will be sent via email. There is requirement for notification of revisions to the IRB for full
board approvals for changes that may impact the risk/classification of the project. The IRB does require
notification of unanticipated events or continuing review of a research that is determined full board.

---

### APPLICATION (FULL BOARD)

**Title of Protocol:**
Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures

<table>
<thead>
<tr>
<th>Principal Investigator (PI): Morgan Guerrette, SRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Person personally responsible for the conduct of the research)</td>
</tr>
<tr>
<td>Dept/Address: CMMC Anesthesia Department 300 Main Street Lewiston ME 04240</td>
</tr>
<tr>
<td>Phone: 207-795-2669</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Principal-Investigator (co-PI): Katherine Balzano-Cowan, SRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Person equally responsible for the conduct of the research)</td>
</tr>
<tr>
<td>Dept/Address: CMMC Anesthesia Department 300 Main Street Lewiston ME 04240</td>
</tr>
<tr>
<td>Phone: 207-795-2669</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sub-Investigator: Tina Moring, Sarah Green, James Osgood, Elizabeth Turcotte</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Person who is a member of the research team designated and supervised by the investigator to perform study-related procedures and/or to make important study-related decisions)</td>
</tr>
<tr>
<td>Dept/Address: CMMC Anesthesia Department 300 Main Street Lewiston ME 04240</td>
</tr>
<tr>
<td>Phone: 207-795-2669</td>
</tr>
</tbody>
</table>

### Funding/Protocol Information

- Who wrote the protocol or plan for this study? (please choose only one)
  - [ ] Funder/Sponsor (listed below under C)
  - [ ] Cooperative Group PI:
  - [x] Principal Investigator: (listed above)
  - [ ] Other:

- Is this protocol being supported by a federal funding agency or non-funded e.g. NIH, AHA, etc.?
  - [ ] Yes  [x] No

  If yes, please provide a copy of the entire Grant (research plan) for review.

- What funding agency is supporting your protocol:
  - Grant Title:

- Is this protocol being sponsored by an Industry (Pharmaceutical or Device) Sponsor?
  - [ ] Yes  [x] No

(Please list the company below, even if you are not receiving monetary support.)
### Name of Industry Funder/Sponsor:

<table>
<thead>
<tr>
<th>Contact Person &amp; Title:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td></td>
</tr>
<tr>
<td>Address:</td>
<td></td>
</tr>
<tr>
<td>Phone:</td>
<td></td>
</tr>
<tr>
<td>Fax:</td>
<td></td>
</tr>
</tbody>
</table>

If this protocol is not being funded by either a funding agency, or an industry sponsor, please indicate where the funding for the conduct of this protocol is being obtained (if any):

- [ ] Non-Funded
- [ ] Departmental Funding
- [x] Cooperative Group

#### Location of Research

<table>
<thead>
<tr>
<th>Where will the study take place?</th>
<th>Central Maine Medical Center</th>
</tr>
</thead>
</table>

Will the PI be conducting and/or supervising study related activity at any sites not under the jurisdiction of this IRB/Privacy Board?

- [ ] Yes
- [x] No

If yes, please attach to this application and provide name and address for each location AND documentation of approval to conduct the research at these sites.

---

**Note:** CMHC IRB approval of your protocol does not include permission to perform any protocol-related activities at these sites. Additional IRB approval may be required from these sites.

---

#### Will this study require hospital admission?

- [x] Yes
- [ ] No

If yes, you must notify the Admissions Department at 755-3892 after IRB approval.

#### Do you have attending privileges at CMHC (CMMC, Rumford Hospital, Bridgton Hospital)?

- [ ] Yes
- [x] No

#### Are you an employee of CMHC (CMMC, Rumford)

- [x] Yes
- [ ] No
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital, Bridgton Hospital?</td>
<td>No, to both question you must have a CMHC sponsor.</td>
</tr>
<tr>
<td></td>
<td>Please provide the name of that person:</td>
</tr>
<tr>
<td></td>
<td>Tina Moring</td>
</tr>
<tr>
<td>Subject Information</td>
<td></td>
</tr>
<tr>
<td>Subjects will be: (check all that apply)</td>
<td>☒ Inpatients ☐ Outpatients</td>
</tr>
<tr>
<td></td>
<td>☐ Non-Patients ☒ Males ☒ Females</td>
</tr>
<tr>
<td>Will subjects who do not understand English be enrolled?</td>
<td>☒ Yes ☐ No</td>
</tr>
<tr>
<td></td>
<td>If yes, describe your resources to communicate with these subjects:</td>
</tr>
<tr>
<td></td>
<td>Indemand interpreting services</td>
</tr>
<tr>
<td>Potentially Vulnerable Populations:</td>
<td>☐ Children ☒ Prisoners ☒ None</td>
</tr>
<tr>
<td></td>
<td>☐ Students ☒ Pregnant Women</td>
</tr>
<tr>
<td></td>
<td>☐ Other(describe):</td>
</tr>
<tr>
<td>Recruitment</td>
<td></td>
</tr>
<tr>
<td>How many subjects does your site anticipate recruiting?</td>
<td>125</td>
</tr>
<tr>
<td>Who will be approaching potential subjects for informed consent?</td>
<td>Dr. David Brown MD</td>
</tr>
<tr>
<td></td>
<td>Dr. Jeffrey Bush MD</td>
</tr>
<tr>
<td></td>
<td>Dr. Matthew Bush MD</td>
</tr>
<tr>
<td></td>
<td>Dr. Paul Cain MD</td>
</tr>
<tr>
<td></td>
<td>Dr. Patrick Fallon MD</td>
</tr>
<tr>
<td></td>
<td>Dr. Michael Regan MD</td>
</tr>
<tr>
<td></td>
<td>Dr. James Timoney Do</td>
</tr>
<tr>
<td>How much time will subjects have to make a decision about study</td>
<td>15 min</td>
</tr>
<tr>
<td>participation?</td>
<td></td>
</tr>
<tr>
<td>Potentially Vulnerable Populations:</td>
<td>☐ By chart/database review</td>
</tr>
<tr>
<td></td>
<td>☐ Course participants</td>
</tr>
<tr>
<td></td>
<td>☐ From the Investigator’s own patients</td>
</tr>
<tr>
<td></td>
<td>☐ Living conditions (street, nursing home)</td>
</tr>
<tr>
<td></td>
<td>☐ Referrals</td>
</tr>
<tr>
<td></td>
<td>☐ Circumstance (i.e. hospital admission, homeless)</td>
</tr>
<tr>
<td></td>
<td>☐ Describe any other sources:</td>
</tr>
<tr>
<td></td>
<td>☐ Direct Advertising</td>
</tr>
<tr>
<td></td>
<td>List here:</td>
</tr>
<tr>
<td>How will subjects be identified as potential research subjects?</td>
<td>When CMO is consulted for ORIF of hip fracture in the emergency room</td>
</tr>
<tr>
<td>How will subjects be recruited for participation?</td>
<td>☐ At a scheduled visit by the investigator</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Who is the custodian of the above indicated chart(s) / database(s) used for recruitment?

- Surgeons

Describe how the custodian is going to contact the subject(s).

- Via consent/flagged in the ED prior to surgery

---

**Initial contact to potential subjects must be made by the custodian of the chart(s)/database(s). Please attach any letters, ads or other information that will be sent to the subjects.**

**Direct advertising** for subject recruitment includes:

<table>
<thead>
<tr>
<th>Radio</th>
<th>Television</th>
<th>Letters to patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newspaper</td>
<td>Bulletin board / flyer</td>
<td>None</td>
</tr>
<tr>
<td>Internet</td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

(continued)

**APPLICATION (FULL BOARD)**

---

**Payment to Subjects**

<table>
<thead>
<tr>
<th>Will subjects be paid for participation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Yes  ☒ No</td>
</tr>
</tbody>
</table>

If yes, indicate total amount, (dollar or equivalent):

---

Form of Payment:

(Payment includes all types of reimbursement such as fares, parking fees, etc.)

---

Explain how payments will be made and if the payments are prorated please explain why?

---

Are there any services that will be provided without charge?

| ☐ Yes  ☒ No |

Explain these services if answer is yes:

---

**Type of Research**

<table>
<thead>
<tr>
<th>Are there any services that will be provided without charge?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Yes  ☒ No</td>
</tr>
</tbody>
</table>

If yes, name of radioactive drug(s):

---

<table>
<thead>
<tr>
<th>Does study involve the administration of radioactive drug(s)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Yes  ☒ No</td>
</tr>
</tbody>
</table>
### Does study involve additional x-ray procedure(s)?
- Yes
- No

If yes, name of procedure(s):
Number of procedures:

### Does study involve psychological tests?
- Yes
- No

If yes, tests to be used:

(continued)

#### APPLICATION (FULL BOARD)

### Type of Research

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the study involve the use of questionnaires?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>If yes, provide copies of the questionnaires.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does study involve the use of discarded human tissue/fluids?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Does study involve the use of fetal and abortus tissues?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Does study involve surgical procedures?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If yes, procedures to be used: ORIF of hip fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does study involve dental procedures?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If yes, procedures to be used:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does study involve videotaping/audiotaping or use of photographs</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Does study involve blood draws?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Separate draw for research purposes, or Additional draw during diagnostic testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount per draw: ml # of draws:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the study involve any procedures/tests that are not included above?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If yes, include a list of these procedures/tests:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this study already open nationally?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
If yes, include all updates and Data Safety Monitoring Board (DSMB) reports. Past individual Adverse Event Reports are not necessary.

(continued)

APPLICATION (FULL BOARD)

**Does this Project Involve Investigational Drugs/Devices (IND/IDE)**

- Yes
- No

If yes complete this section and submit an Investigational Drug or Device Data Form.

<table>
<thead>
<tr>
<th>This study involves a drug or biologic:</th>
<th>IND#:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>This study is:</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
<th>Treatment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>This study involves a device:</th>
<th>IDE#:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>This device is:</th>
<th>Investigational</th>
<th>Humanitarian exemption</th>
<th>Marketed</th>
<th>Significant Risk Device</th>
<th>Non-Significant Risk Device*</th>
</tr>
</thead>
</table>

*Sponsor must include justification on Non-Significant Risk per 21 CFR 812.66

**Please Provide Brief Synopsis of Protocol below:**

**Summary of Protocol is Attached**

The undersigned accepts responsibility for assuring that with regard to this protocol, all applicable FDA and HHS regulations and Institutional Policies relative to the protection of the rights and welfare of human research participants are adhered to.

Morgan Guerrette
2016
Signature

October 14,
Date

Morgan Guerrette
Principle Investigator
Print Name
Title

The undersigned acknowledges a review and examination of this research proposal has been completed and assures that this study is appropriate to be conducted at CMHC and that all funding, staffing and budgetary concerns will be approved before enrollment begins. This authorization is required before the Principal Investigator can submit this project to the IRB for review.

Signature of Chair/Vice-Chair
Date

(continued)
**HIPAA waiver criteria** (check all that apply)

| If “PHI” being used? …. (see list of identifiers attached) | □ Yes (If “Yes” please include HIPAA authorization language in the informed consent) |
| Is HIPAA Authorization language required? | ☒ No (Can only be “No” if *Informed Consent waiver and *HIPAA waiver criteria are met) |
| The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on at least the presence of all the following elements: | |
| Is a Limited Data Set (see below list) being used? | □ Yes ☒ No |
| (If “Yes”, provide a copy of the executed Data Use Agreement.) |

**Data Use Agreement** - An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected

**Limited Data Set with Data Use Agreement**

A data set that **excludes** the following direct identifiers can be considered a Limited Data Set:

| Names | Certificate/license #s |
| Postal address info (if other than city, town, state, and ZIP) | VIN and Serial #s, license plate #s |
| Telephone and fax #s | Device identifiers, serial #s |
| E-mail address | Web URLs |
| Social Security # | IP address #s |
| Medical record numbers | Biometric identifiers (finger prints) |
| Health plan #s | Full face photographic images and any comparable images |
| Account #s |

The Limited Data Set **CAN** contain:

- Elements of Dates i.e. Admission, Discharge, Service and Death Dates
- City, Town, State and Zip Code(s)
- Other unique identifiers, characteristics and codes not previously listed as direct identifiers

- There is an adequate plan to protect the identifiers from improper use and disclosure. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

**Describe your plan:**

(continued)

APPLICATION (FULL BOARD)

and

- Adequate written assurance that the protected health information will not be reused or disclosed to
any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use and disclosure of protected health information would be permitted by this subpart.

Describe your plan:

or

☐ The research could not practically be conducted without the HIPAA waiver or alteration.

Provide explanation:

or

☐ The research could not practically be conducted without access to and use of the protected health information.

Provide explanation:

---

List of Identifiers Related to PHI

<table>
<thead>
<tr>
<th>Names</th>
<th>Health plan beneficiary numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic subdivisions smaller than a state</td>
<td>Account numbers</td>
</tr>
<tr>
<td>Zip Codes</td>
<td>Certificate and license numbers</td>
</tr>
<tr>
<td>Dates (birth, admission, discharge, death)</td>
<td>Vehicle identification and serial numbers</td>
</tr>
<tr>
<td>Age, if over 90</td>
<td>License plate numbers</td>
</tr>
<tr>
<td>Telephone numbers</td>
<td>Device identifiers and serial numbers</td>
</tr>
<tr>
<td>Fax numbers</td>
<td>URLs</td>
</tr>
<tr>
<td>E-mail addresses</td>
<td>Internet Protocol address numbers</td>
</tr>
<tr>
<td>Social Security numbers</td>
<td>Biometric identifiers (finger and voice prints)</td>
</tr>
<tr>
<td>Medical Record numbers</td>
<td>Full face photos and comparable images</td>
</tr>
<tr>
<td>Health plan beneficiary numbers</td>
<td>Any other unique identifiers</td>
</tr>
<tr>
<td>Account numbers</td>
<td></td>
</tr>
<tr>
<td>Certificate and license numbers</td>
<td></td>
</tr>
<tr>
<td>Vehicle identification and serial numbers</td>
<td></td>
</tr>
<tr>
<td>License plate numbers</td>
<td></td>
</tr>
<tr>
<td>Device identifiers and serial numbers</td>
<td></td>
</tr>
<tr>
<td>URLs</td>
<td></td>
</tr>
<tr>
<td>Internet Protocol address numbers</td>
<td></td>
</tr>
<tr>
<td>Biometric identifiers (finger and voice prints)</td>
<td></td>
</tr>
<tr>
<td>Full face photos and comparable images</td>
<td></td>
</tr>
<tr>
<td>Any other unique identifiers</td>
<td></td>
</tr>
</tbody>
</table>

If PHI is being used and not part of a Limited Data Set is the data going outside of CMHC? ☐ Yes ☐ No

(If “Yes”, please provide a copy of an executed Business Associate Agreement.

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APPLICATION (FULL BOARD)

Identify Activities Preparatory to Research

For activities involved in preparing for research, covered entities may use or disclose PHI to a researcher without an individual’s Authorization, a waiver or an alteration of Authorization, or a Data Use Agreement. However, the covered entity must obtain from a researcher representations that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research. The covered entity may permit the researcher to make these representations in written or oral form.
Please describe this use and disclosure of PHI:

According to HHS guidance on the Privacy Rule, the preparatory to research provision permits covered entities to use or disclose protected health information for purposes preparatory to research, such as to aid study recruitment. However, the provision at 45 CFR 164.512(i)(1)(ii) does not permit the researcher to remove protected health information from the covered entity's site. As such, a researcher who is an employee or a member of the covered entity's workforce could use protected health information to contact prospective research subjects [emphasis added]. The preparatory research provision would allow such a researcher to identify prospective research participants for purposes of seeking their authorization to use or disclose protected health information for a research study.

☐ Yes, I agree to the above.

__________________________  __________________________
Signature                      Date

__________________________  __________________________
Print Name                    Title

continued)

APPLICATION (FULL BOARD)

FOR IRB USE ONLY

Is an Informed Consent Required?

☐ Yes  ☐ No (Research meets all four CFR *ICF waiver criteria listed below)

Informed consent waiver criteria (check all that apply)

☐ The research involves no more than minimal risk to the subjects,
☐ The waiver or alteration will not adversely affect the rights and welfare of the subjects,
☐ The research could not practicably be carried out without the waiver or alteration, and
☐ Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

DETERMINATION

☐ Informed Consent and HIPAA waiver criteria are met and Waiver of Authorization was approved

IRB Recommendation:
This project is approved
☐ This project is not approved; further details provided within IRB’s determination letter.

Certification: I have reviewed the above-captioned protocol for general scientific & medical validity and safety.

__________________________________________  ____________________________
Signature                                      Date

__________________________________________  ____________________________
Print Name                                    Title

IRB REVIEW FEE POLICY

It is a standard practice among Institutional Review Boards to charge a fee to commercial sponsors for new studies reviewed by the full Board, new studies that can be reviewed as expedited and studies that are up for a continuing review.

Effective January 2010, the IRB fees are as follows:

- $2,000.00 fee (increased from $1,750.00) for new studies reviewed by the full Board,
- $500.00 fee (no fee increase) for new expedited studies reviewed (protocols reviewed by a single IRB reviewer),
- $250.00 fee (new fee) for all continuing reviews or amendments whether full Board or Expedited.

These fees do not currently apply to non-funded, or federally-funded research. IRB initial review applications will request sponsor billing information for the billing of these fees with an expectation that the Study Coordinators/Principal Investigators will notify the IRB of any address changes for billing. The IRB Administrator will forward a copy of the billing information to the Director of Research who will process the bill with the sponsor. Once CMHC receives the IRB fee either the Director of Research or Accounts Payable office will notify the IRB Administrator payment has been received. **This fee is for IRB review and is not contingent upon approval.**

Upon notice by the Principal Investigator the IRB may waive this fee if the IRB finds the fee would create a meaningful obstacle to research conduct.

Billing Contact Person Name:  Phone:
<table>
<thead>
<tr>
<th>For office Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB#:</td>
</tr>
<tr>
<td>Protocol Entitled [as given above]:</td>
</tr>
<tr>
<td>Account No:</td>
</tr>
<tr>
<td>Billing Information:</td>
</tr>
<tr>
<td>Fee for IRB processing of Principal Investigator:</td>
</tr>
</tbody>
</table>
Central Main Medical Center
300 Main Street
Lewiston, Maine 04240

To: Lois Downs, IRB
From: Dr. Jeffrey Bush

October 17, 2016

Re: Research Support- Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures

This letter is to inform the Institutional Review Board (IRB) at Central Maine Medical Center that I am in full support of the work that Morgan Guerrette and Katherine Balzano-Cowan have presented to the IRB with regards to the “Tranexamic Acid research study to reduce blood transfusion in hip fractures” (TXA). This proposed research project is to examine if administration of TXA in hip fractures reduces the percentage of patients requiring blood transfusions. Currently, TXA is being utilized for total joints at Central Maine Medical Center and studies have shown its benefits in a reduction of blood utilization in hip fractures.

The research involves individuals who are 65 years of age or older and have a hip fracture. The patient will then be screened according to inclusion and exclusion criteria identified in the study. Patients who meet criteria will then be given education on the study and if they are willing participants will have informed consent. The study will be coordinated out of Central Maine Medical Center. There are no funding sources for this project. I consider this work important in supporting clinical practice and identifying evidence-based outcomes that will influence patient care. I believe our patients will benefit from the research questions answered by this study. Please do not hesitate to contact me if the IRB requires additional information. Thank you.

Sincerely,

Dr. Jeffrey Bush
Central Maine Orthopedics
October 16, 2016

Dear Institutional Review Board Committee Members,

This letter is to inform you that no conflict of interest exists between Kate Balzano-Cowan and Morgan Guerrette regarding our involvement with the project: Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures. No promises of profit or advantage were made from Central Maine Medical Center for the work provided to this project. Additionally, participation in this project does not guarantee a positive outcome or passing grade from the University of New England concerning our Senior Capstone Project or other classroom work.

Sincerely,

Morgan Guerrette and Kate Balzano-Cowan
TRANEXAMIC ACID AND HIP FRACTURES

WHAT IS TRANEXAMIC ACID?
Tranexamic acid (TXA) is given through an IV to prevent or reduce bleeding and reduce the need for blood transfusions during a trauma or surgery.

WHY IS THIS STUDY BEING DONE?
This research is being done because we have seen excellent results using tranexamic acid during scheduled hip and knee replacements. Research has shown patients receiving tranexamic acid before scheduled surgery to replace hip and knee joints bleed less. We hope that using this drug in traumatic hip fractures will give patients the same benefit.

ARE THERE BENEFITS TO TRANEXAMIC ACID?
Tranexamic acid has been shown in other research to reduce bleeding and the need to be given blood from another person after traumatic accidents and before planned hip and knee replacement surgeries.

ARE THERE RISKS AND SIDE EFFECTS OF TRANEXAMIC ACID?
Risks and side effects related to giving tranexamic acid to reduce blood loss might include: Adverse vascular event including, but are not limited to, myocardial infarction (very rare but serious), symptomatic DVT (less likely but serious), or pulmonary embolism (less likely but serious).

For more information about risks and side effects, and/or to report side effects and adverse events. Please speak to the researcher or contact Elizabeth Turcotte, RN via phone (207.795.2134) or email (TurcotEl@cmhc.org).
TXA Fracture Study

January 2017
CMMC-OICM-CMO-UNE

TXA: Current Uses

- Total knee replacements
- Total hip replacements
- Literature demonstrates TXA reduces blood product utilization
- Nationally being widely utilized for traumas etc...
- CRASH2 study

TXA: Hip Fracture Study

- GOAL: to see a decrease in blood utilization and better outcomes for patients with hip fracture
- Starting January 11, 2017
- Patients with fractured hips can be entered into TXA study
- Each patient receives a hospitalist consult
- Based on patient history they can either be included in the study or excluded

Inclusion/Exclusion Criteria

Inclusion Criteria:
- Any patient over age 50 with hip fracture
- Gives consent to participate in the study

Exclusion Criteria:
- Anticoagulated
- History of vascular events:
  - stroke
  - myocardial infarction
  - pulmonary embolism
  - deep vein thrombosis
  - clotting disorder
- Patients with either unknown or if a full medical history can not be obtained
Process

- Patient receives hospitalist consult at admission
- Determined to be either potential inclusion or ruled an exclusion
- Patient will receive a packet and face to face time to complete the informed consent

Consents

- Patients selected as “meets criteria” for inclusion:
  - Patient/POA will be educated - literature and discussion about what is TXA, risks, benefits
  - If they choose to enroll in the study - consent will be obtained
  - “Study drug” will be ordered and patient will receive either TXA or placebo

Who orders the drug?

- Ideally the surgeon will order the drug
- The drug is ordered by entering the words “study drug”
- If the surgeon is not able to order the drug, the Clinical Coordinator or the CRNA will order the drug as a verbal order under the surgeon
- The pharmacy will send the “study drug” as an on call medication when the patient is going to the OR

Who gets Consents

- Consents can only be obtained by those who are listed on the IRB application
- Surgeons CMO/Clinical Coordinators M2/Jim Osgood or Tina Moring/Morgan Guerrette or Kate Balzano-Cowan
  - Primarily Clinical Coordinators during weekday hours
  - Jim Osgood or Tina Moring on weekend hours
What do we need to know?

- Starting in 2017 TXA for fractured hips may be given – “Study Drug”
- It is a one-time dose much like TXA for total hips now
- Sign off on the MAR as “study drug”
- Either TXA or Placebo drug will be administered
- Providers (surgeons, nurses, CRNA) will be blinded as to what the patient has received: either TXA or placebo

Post Op

- Post op patients will be entered into a data base and tracked for blood product utilization and/or complications
- Data will be followed for approximately 1 year
- Communicate with PACU/Post op team that patient was enrolled in the “study”
- Goals: see a decrease in blood product utilization and better outcomes for patients with hip fracture
Central Maine Healthcare Corporation
Authorization to Participate in a Research Project

STUDY TITLE: Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures

IRB NUMBER: 494

CONSENT VERSION DATE: 10.09.2016

HOSPITAL OR INSTITUTION: Central Maine Medical Center

INVESTIGATOR: Morgan Guerrette

SUBJECT’S NAME (printed):

You are being asked to volunteer for a research study. Research studies include only patients who choose to take part. In order to decide whether you should agree to be part of this research study, you should understand enough about its risks and benefits to make an informed choice. This process is known as informed consent. Please take your time to make your decision. If we are unable to obtain a full medical history, you will be excluded from this study.

You are being asked to take part in this study because you have sustained a traumatic fracture to one of your hip joints.

WHY IS THIS STUDY BEING DONE?
This research is being done because we have seen excellent results using tranexamic acid during scheduled hip and knee replacements. Research has shown patients receiving tranexamic acid before scheduled surgery to replace hip and knee joints bleed less. We hope that using this drug in traumatic hip fractures will give patients the same benefit.

HOW MANY PEOPLE WILL TAKE PART IN THE CLINICAL TRIAL?
Up to 125 people will take part in this study. Central Maine Medical Center is the only site approved to enroll people into this study.

WHAT IS INVOLVED IN THE STUDY?
If you decide you would like to participate in this study, you will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer decides which group you are put in. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in any one group. The groups are: The control group or the drug-receiving group. Patients in the control group will be treated in the same way as all patients coming to the hospital with broken hips are presently treated. Patients in the control group will not receive tranexamic acid before having surgery to repair their broken hip. Patients in the
drug-receiving group will be given 1 gram of tranexamic acid before having surgery to repair their broken hip.

- Standard procedures and tests that will be done during the trial which are part of the regular care of a patient with a hip fracture are complete blood counts done the day of your surgery and at regular intervals after surgery as determined by your doctor.

- There are no additional standard procedures or tests that will be done during the trial that are being done because of participation in the trial.

- Should you be randomized into the drug-receiving group, giving you the tranexamic acid prior to your hip surgery is the only procedure/test that is considered experimental and being tested in this trial.

**HOW LONG WILL I BE IN THE STUDY?**
We think you will be in the study for the length of your admission to the hospital to have your broken hip fixed.

Should you decide to take part in this study, there is no reason the researcher may decide to take you off this study.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first. There are no serious consequences of sudden withdrawal from the study and there are no additional testing or procedures that would need to be done in order for you to safely withdraw from this study.

**WHAT ARE THE RISKS OF THE STUDY?**
While in this study, you are at risk for these side effects listed below. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict; in some cases side effects can be serious or long lasting or permanent.

Risks and side effects related to giving tranexamic acid to reduce blood loss might include:
Adverse vascular event including, but are not limited to, myocardial infarction (very rare but serious), symptomatic DVT (less likely but serious), or pulmonary embolism (less likely but serious).

For more information about risks and side effects, and/or to report side effects and adverse events speak to the researcher or contact Elizabeth Turcotte, RN via phone (207.795.2134) or email (TurcotEl@cmhc.org).

**ARE THERE BENEFITS TO TAKING PART IN THE CLINICAL TRIAL?**
You may benefit from the being given tranexamic acid prior to your hip surgery provided to you by this research. Tranexamic acid has been shown in other research to reduce bleeding and the need to be given blood from another person after traumatic accidents and before planned hip and knee replacement surgeries.

**WHAT OTHER OPTIONS ARE THERE?**
Instead of being in this study, you have the option to decline and will be treated in the same way as patients randomized into the control group of this study.
Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. All of your personal and medical data will be handled in the same way all other personal and medical data at Central Maine Medical Center is handled. Your agreement to take part in this study does not mean you agree to have your personal information disclosed. If you choose to withdraw from the study, you may revoke your approval for the use of your future medical information. To do this, you may contact the researcher in writing. Data which has already been collected, will be maintained with the research records. Study information collected up to that point will be forwarded to the study sponsor. No further study information will be collected after you withdraw from the study.

**WHAT ARE THE COSTS?**
You or your insurance company will not be charged for any tests or services specifically required by this research study unless the tests or services are clinically indicated or part of your standard treatment. You will still be responsible for the cost of your usual ongoing medical care, including procedures, non-study medications, and tests that your study doctor or regular doctor requires during this study as part of your usual medical care.

In the case of injury or illness resulting from this clinical trial, emergency medical treatment is available, but will be provided at the usual charge. Central Maine Medical Center will not compensate you or your insurance company in the event of any injury.

Central Maine Medical Center is not being compensated for their participation in this research study by the study.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**
Taking part in this study is your choice. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your willingness to stay in this study.

**PERMISSION TO USE OR RELEASE IDENTIFIABLE HEALTH INFORMATION FOR RESEARCH PURPOSES**

**WHY AM I BEING ASKED TO RELEASE THIS INFORMATION?**
As part of this clinical trial, you are being asked to allow Morgan Guerrette to collect health information about yourself. This information will be collected, entered onto a database with the health information from others taking part in this clinical trial, and studied to see if giving tranexamic acid before surgery to patients who have broken their hip in a fall lowers their need to be given blood products from other people. Morgan Guerrette may also need to obtain copies of any medical records you have with other health care providers.

**WHAT AM I BEING ASKED TO RELEASE?**
For this clinical trial, the following information will be collected:

- Your date of birth
- Your past medical history
- Your weight, blood pressure, temperature, lab results, and the results of your physical examination during your admission to Central Maine Medical Center to get your broken hip fixed.
WHO WILL SEE THIS INFORMATION?
Personnel or members of the Central Maine Medical Center Institutional Review Board or personnel from the Office of Human Research Protections may see parts of your medical records related to this clinical trial and, therefore, will see your name and other personally identifiable information about you. The information collected is the property of Morgan Guerrette, and you will not be able to get it back.

WILL THE INFORMATION COLLECTED AS PART OF THIS STUDY BE DESTROYED WHEN IT IS NO LONGER NEEDED?
In the event of any publication regarding this study, your identity will not be disclosed. It is difficult for Morgan Guerrette to know how long your information will be kept at least until the end of the clinical trial, but most likely it will be kept on a database within the Anesthesia Department at Central Maine Medical Center for an indefinite length of time. We do not know when your information will no longer be used, and there is not expiration date after which it will be discarded.

CAN I STOP MY INFORMATION FROM BEING USED?
If you choose to withdraw from the study, you may revoke your approval for the use of your future medical information. To do this, you may contact the researcher in writing. Data that has already been collected will be maintained with the research records. Study information collected up to that point would be forwarded to the study sponsor. No further study information will be collected after you withdraw from the study.

During the study, you may not have access to your information through the researcher but you may request information after research is completed. All information collected as part of this study will be part of your medical record at Central Maine Medical Center. Should you wish to obtain your information through the hospital please contact Medical Records Department and follow their instructions.

WHAT IF I DO NOT AUTHORIZE YOU TO COLLECT AND RELEASE MY HEALTH INFORMATION?
If you agree to be in this clinical trial, you are authorizing the release of your health information as part of the trial. Participants will be given a copy of the signed consent document for their own records. If you do not want to release your health information, you may not want to take part in this clinical trial (do not sign this form if you do not want to take part in this clinical trial, or you do not want to release your health information).

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury contact Elizabeth Turcotte via phone (207.795.2134) or email (TurcotEl@cmhc.org).

For questions about your rights as a research participant, contact the Central Maine Medical Center Institutional Review Board (which is a group of people who review the research to protect your rights) at (207) 795-2176. Deborah Taylor, Ph.D. is the chairperson of the Central Maine Medical Center Institutional Review Board.

COMPENSATION
Participants in this study will not receive any compensation if the results of the research are used towards the development of a commercially available product.
A description of this clinical trial will be available on [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this site at any time pursuant to 21 CFR 50.25(C). For applicable clinical trials as defined in 42 U.S.C. 282(j)(1)(A).

You have read, or have had read to you, the above information before signing this consent form. You agree to participate in this clinical trial. You also authorize you your permission to use or disclose your personal health information for the purpose of this research. You have been offered ample opportunity to ask questions and have received answers that fully satisfy those questions.

I have agreed to participate in this research project. I understand the purpose of the procedure(s) and the risks/benefits involved in its performance.

__________________________________________  _________________________
Signature of Participant or guardian                            Date

__________________________________________
Printed Name of Participant or guardian

I have fully explained to ____________________ the nature and purpose of the above-described procedure and the risks/benefits involved in its performance. I have answered and will answer all questions to the best of my ability. I will inform the subject of any changes in the procedure or the risks and benefits if any should occur during or after the course of the study.

__________________________________________  _________________________
Signature of person obtaining consent                            Date
Appendix E

Approval Letter

Central Maine Healthcare Corporation
INSTITUTIONAL REVIEW BOARD
Central Maine Medical Center, Bridgton Hospital, and Rumford Hospital

Deborah Taylor, Ph.D., IRB Chair
Jenae Limoges, MD, IRB Vice-chair
Phone: (207) 795-8246
Fax: (207) 344-0373

Lois N. Downs, IRB Administrator
Risk Management
300 Main Street
Lewiston, Maine 04240

Today's Date: November 17, 2016
Date of Determination: November 17, 2016
To: Principal Investigator, Morgan Guerrette, CRNA
IRB #: 494
Status of Initial Review on 11/17/2016: Approved ( Expedited)
Date of Current Informed Consent: 11/17/2016

<table>
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<tr>
<th>2016</th>
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<tbody>
<tr>
<td>Initial Review Submission to the IRB: 10/19/2016</td>
<td>Continuing Review Submission to the IRB:</td>
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<td>Date of Determination: 11/17/2016</td>
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<td>IRB's Next Scheduled Continuing Review: 11/17/2017</td>
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STUDY TITLE: Utilizing Tranexamic Acid to Reduce Blood Transfusion in Hip Fractures

The Central Maine Healthcare Institutional Review Board (IRB) Chair did an Initial Review on your Full Board Application and "approves" your protocol as an “Expedited” study since the study design is already well studied in elective joints, and is reported to be safe; extending it to fractures reportedly is not of high risk. The Chair determined that this study falls under the Expedited Category 45 CFR 46.101(b)(4) as follows:

Collection of data through, noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) EXAMPLES: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

The documents reviewed and approved:
- Application;
- Protocol;
- Informed Consent;
- NIH and HIPAA Certificates;
- Conflict of Interest Forms;
- Patient Handout;
- Letter of Support from Jeffrey Bush, M.D.; and
- CVs.

Please note this approval is valid until November 17, 2017. On or before this date the IRB Chair or Vice Chair will review the protocol. Prior to that date you will be asked to provide a Continuing Review Progress Report for this project.

It is the responsibility of the Morgan Guerrette, CRNA to notify the IRB of all unanticipated serious adverse events and deviations encountered in this study in a prompt manner. Any changes or modifications to the study protocol must be in writing to the IRB for review prior to implementation.

If you have any questions, please contact the IRB office at 207-795-8246.

Sincerely,

[Signature]
Deborah A. Taylor, Ph.D.