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Tranexamic Acid in Radical Resection and Endoprosthetic Reconstruction Protocol

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University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS TEMPLATE WITH GUIDANCE

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Principal Investigator: Kyle Sweeney MD, Assistant Professor of Orthopaedic Surgery

Study Title: Tranexamic Acid in Radical Resection and Endoprosthetic Reconstruction: A Randomized Controlled Trial

Co- Investigator(s): Howard Rosenthal MD, Kimberly Templeton MD, Jacob Birlingmair MD

I. Purpose, Background and Rationale A. Aim and Hypotheses

Resection of bony and soft tissue tumors with endoprosthetic reconstruction presents a significant risk of perioperative blood loss requiring transfusion. As transfusions are known to have inherent risks, a goal of therapy is to minimize perioperative blood loss. Tranexamic acid (TXA) is an antifibrinolytic that is commonly used to reduce blood loss in orthopaedic procedures, most often arthroplasty. The safety (even in patients with significant comorbidities) and efficacy of TXA in joint arthroplasty is well documented in the literature. There is, however, a dearth of literature exploring the safety and efficacy of TXA in musculoskeletal oncologic patients.

The aim of this study is to determine in a randomized controlled fashion if there is any difference in perioperative blood loss and blood transfusion rates when tranexamic acid is used compared to when it is not used in patients undergoing radical resection of bone and soft tissue sarcomas with endoprosthetic reconstruction. Hypotheses: (1) TXA will decrease perioperative blood loss. (2) TXA will decrease blood transfusion rates. (3) TXA will decrease post-operative surgical drain output.

B. Background and Significance

Study Significance: The large bony and soft tissue tumor resections performed in musculoskeletal oncologic patients presents the potential for significant blood loss. With basic arthroplasty being associated with significant intraoperative and postoperative blood loss often necessitating blood transfusion[1], larger bony resections with the use of endoprostheses presents an even higher risk[2]. Transfusions themselves are not without known complications. Examples include infection, hemolytic transfusion reaction, and increased short-term mortality[1,3]. Tranexamic acid (TXA), a synthetic analog of lysine, is an antifibrinolytic that is used to reduce blood loss. TXA works by blocking the lysine binding sites on plasminogen[4]. Perioperative use of TXA has been shown to decrease intraoperative and postoperative blood loss and decrease transfusion rates in both total knee arthroplasty and total hip arthroplasty[5-15]. It has also been shown to result in higher postoperative hemoglobin[13]. TXA also has been shown to decrease postoperative pain, swelling, length of hospital stay, and result in higher patient satisfaction[16]. The proposed research is intended to show if any correlation exists between administration of TXA or not to musculoskeletal oncology patients undergoing endoprosthetic reconstruction and perioperative blood loss and blood transfusion rates. The results of this study are

important because it will serve to fill the void in the current literature as there is no current literature available that has studied TXA administration in this specific patient population.

There have been several papers written with regards to the safety of TXA in high risk patients (i.e. previous PE/VTE event).[21,22] Whiting et al showed that in high risk patients (defined as American Society of Anesthesiologists score of III or IV) , TXA was not associated with an increase in symptomatic thromboembolic events and was associated with a decrease in transfusion rates.[22] Sabbag et al showed that patients with a history of VTE had a low risk of recurrent VTE (2%) after contemporary total hip arthroplasty and total hip arthroplasty, and that rate was not increased with the use of IV TXA.[21]

Literature Review

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C. Rationale

The large bony and soft tissue tumor resections performed in musculoskeletal oncologic patients presents the potential for significant blood loss. With basic arthroplasty being associated with significant intraoperative and postoperative blood loss often necessitating blood transfusion[1], larger bony resections with the use of endoprostheses presents an even higher risk[2]. Transfusions themselves are not without known complications. Examples include infection, hemolytic transfusion reaction, and increased short-term mortality[1,3]. Tranexamic acid (TXA), a synthetic analog of lysine, is an antifibrinolytic that is used to reduce blood loss. TXA works by blocking the lysine binding sites on plasminogen[4]. Perioperative use of TXA has been shown to decrease intraoperative and postoperative blood loss and decrease transfusion rates in both total knee arthroplasty and total hip arthroplasty[5-15]. It has also been shown to result in higher postoperative hemoglobin[13]. TXA also has been shown to decrease postoperative pain, swelling, length of hospital stay, and result in higher patient satisfaction[16].

This project has the potential to make a profound impact on how musculoskeletal oncology patients undergoing endoprosthetic reconstruction are managed in the perioperative period. This project will advance our knowledge in the musculoskeletal oncology field by potentially showing a significant correlation between administration of TXA and decreased rates of blood transfusions and perioperative blood loss. This has already been shown in the total joint arthroplasty literature. However, there is a lack of available literature that shows the effects of TXA on the patient population we wish to study. Because of this the use of TXA in this patient population is sporadic and varies widely from surgeon to surgeon. Providing a definitive answer regarding the safety and efficacy of TXA in this patient population would both unify the musculoskeletal oncology field in their use or abandonment of TXA, and potentially improve oncologic patient care in a similar fashion than that seen with the use of TXA in arthroplasty. The clinical outcomes that are evaluated by this project have the potential to make a profound impact on the lives of the patients we care for on a day-to-day basis.

This project has the potential to improve clinical outcomes of musculoskeletal oncology patients undergoing endoprosthetic reconstruction with TXA. Examples of potential improved clinical outcomes that could be derived from this project are: decreased intraoperative and postoperative blood loss and decreased transfusion rates with administration of TXA in this specific patient population.

II. Research Plan and Design

A. Study Objectives: Specific Aims: to determine if there is any significant difference in perioperative blood loss and blood transfusion rates when TXA is used compared to when it

is not used in patients undergoing radical resection of bone and soft tissue sarcomas with endoprosthetic reconstruction. Statement of Purpose: to determine in a randomized controlled fashion if there is any difference in perioperative blood loss and blood transfusion rates following radial resection of malignant bony tumors with endoprosthetic reconstruction when TXA is used compared to when it is not. Primary outcome measure: determination of perioperative blood loss. To do this, values will be recorded preoperatively and compared to post-operative values. Perioperative blood loss will be calculated using the Hemoglobin balance method.[23-26] Secondary outcome measures: (1) Blood transfusion rates. (2) Surgical drain output.

B. Study Type and Design: Type of Study: multi-center prospective randomized controlled trial. Study Design: We will initially monitor 4 groups of patients. The first group (20 patients) will undergo bony tumor resection of the femur or proximal tibia and endoprosthetic reconstruction with TXA. The second group (20 patients) will undergo bony tumor resection of the femur or proximal tibia and endoprosthetic reconstruction without TXA. The third group (50 patients) will undergo soft tissue sarcoma resection of the lower extremity with TXA. The fourth group (50 patients) will undergo soft tissue sarcoma resection of the lower extremity without TXA. The use of TXA is well established for arthroplasty at this institution given the body of evidence supporting both efficacy and safety. Treatment assignments will be stratified by type of resection location. Patient randomization will be done via randomization program through REDCap. The randomization process will be performed centrally at Kansas University Medical Center and the treating surgeon will not have access to the randomization list. Randomization will occur prior to definitive surgical procedure, and the treating surgeon and pharmacy will be notified to ensure adequate vials of tranexamic acid are available in the operating room (investigators/surgeons are not blinded). Patients will be blinded to treatment allocation. Those in groups using TXA will receive 1g TXA IVPB 10 minutes prior to incision and a second dose of 1g IVPB at the time of closure which is the standard protocol used for total joint arthroplasty. The TXA will be administered by the anesthesia team. If the surgeon determines intraoperatively that TXA is required for patient safety, the drug should be used. Patients receiving a non-standard dosing of TXA will then be excluded from the study. Routine hemoglobin and hematocrit measurements will be observed preoperatively as well as postoperatively at 6 hours and in the mornings of postoperative days 1-3. This laboratory regimen is currently the standard of care and utilized routinely. Patients may be discharged prior to obtaining all 4 blood draws. If a patient is discharged prior to postoperative day 3, no additional blood draw will be performed. Additionally, both intraoperative and postoperative incidents of blood transfusion will be monitored to calculate transfusion rates. Postoperative erythrocyte transfusions will be given for hemoglobin below 7.0 as is the current practice guidelines used by the attending surgeons at this institution. Other facilities are encouraged to follow this protocol, however, the ultimate decision for blood transfusion will be at the discretion of the treating physician. Surgical drains are also used routinely and their daily output will be recorded until they are deemed appropriate to pull by the attending surgeon. Patients will be clinically monitored daily while in the hospital and in subsequent follow up visits for symptoms of DVT or embolism and appropriate diagnostic screening with venous Doppler will be utilized if symptoms are present, as is also part of current routine postoperative care. Our DVT prophylaxis protocol postoperatively will be 4 weeks of aspirin 81 mg BID unless medical co-morbitities necessicate the use of other anti-coagulation. Mechanical DVT prophylaxis in the form of sequential compression devices will also be

utilized. We also plan to record patient specific factors including age, sex, smoking status, BMI, pre-op diagnosis, operative time, comorbidities, and length of stay. These variables will be analyzed independently to detect any correlation with perioperative blood loss and erythrocyte transfusion rate.

C. Sample size, statistical methods, and power calculation

Method of Randomization: Patient randomization will be done via a randomization program through REDCap. The randomization process will be performed centrally at Kansas University Medical Center and the treating surgeon will not have access to the randomization list. Randomization will occur prior to definitive surgical procedure, and the treating surgeon and pharmacy will be notified to ensure adequate vials of tranexamic acid are available in the operating room (investigators/surgeons are not blinded). Patients will be blinded to treatment allocation. Treatment assignments will be stratified by type of resection. A power of 0.9 would require a total of 40 patients (20 per treatment group) be enrolled in the bony tumor group and 100 patients (50 per treatment group) in the soft tissue tumor group.

Since we are gathering entirely objective data the treating surgeon does not need to be blinded. Group differences in preoperative hemoglobin and hematocrit, transfusion requirements, drain output at 24 hours, and changes in hemoglobin and hematocrit will be compared using pairwise Student T-test analysis. Pairwise T-tests between each of the groups (for continuous variables) and Chi squared analysis (for categorical variables) will be used to determine if a statistically significant difference exists between the groups in terms of the patient specific factors that are also collected and analyzed (age, sex, smoking status, BMI, operative time, length of stay).

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

Inclusion criteria: Patients (male or female) between the ages of 18-90 undergoing wide resection of a malignant bony tumor of the lower extremity with endoprosthetic reconstruction or resection of soft tissue sarcoma measuring >5cm.

Exclusion criteria:

- Patients undergoing revision endoprosthetic reconstruction
- Patients with known coagulopathy
- Known history of DVT or embolic disease
- Benign tumors
- Patients with allergy to TXA
- Those refusing blood products
- Those concurrently on anti-coagulant therapy
- Pregnant and nursing women
- Vulnerable populations as defined by the University of Kansas Medical Center IRB

Withdrawal/Termination criteria: The subject's participation will be terminated by the investigator if the subject wishes to withdrawal from the study at any point in time. In the event that a disproportionate number of complications are occurring in one of the study groups, the study will be suspended and the IRB will be consulted. There are no

safety precautions that need to be applied to subjects who withdraw from the study. The withdrawn patients will be routinely followed on an outpatient basis in a clinic setting.

E. Specific methods and techniques used throughout the study

1. Laboratory tests: Complete Blood Count (CBC) – the purpose of collection is to help determine the effect of TXA on hemoglobin and hematocrit levels. A CBC would be collected pre-operatively and post-operatively at 6 hours and in the mornings of postoperative days 1, 2, and 3. Patients may be discharged prior to obtaining all 4 blood draws. If a patient is discharged prior to postoperative day 3, no additional blood draw will be performed. Blood specimens will need to be collected for this test. This test is routinely ordered in the hospital setting and is the standard of care for evaluating and monitoring blood loss post-operatively.
2. Study Procedures: Describe each procedure to be used in the study, including the instruments used, time required for each procedure, cognitive assessments, etc. The patient's consented for this study and randomized to the TXA group will receive TXA while in the operating room as part of the routine administration of anesthesia. This is not technically considered a procedure.
3. Clearly indicate which procedures, tests, visits, etc., are parts of usual standard therapy and which are performed solely for research purposes. Make it clear which tests are routinely performed for clinical care but are providing data for the research (and are billable to insurance companies), and which tests are only performed for research purposes (not billable to insurance companies). Usual standard therapy: all postoperative clinic visits, pre-operative and post-operative CBC. These CBCs would be providing data for this clinical trial. No tests will be ordered that are only performed for research purposes.
4. Describe the fate of any body component: No body components will be obtained during this study.
5. Timeline: Patients will be seen at routine post-operative visits at 2-3 weeks, 6 weeks, and 3 months where clinical examination and history taking will take place.

F. Risk/benefit assessment:

1. Physical risk: The primary concern with the use of TXA is the theoretical risk of developing a deep venous thrombosis. The patients will be monitored clinically for signs and symptoms of DVT while they are admitted to the hospital as well as at routine postoperative visits.
2. Psychological risk: We do not anticipate any psychologic risk to participants in this study.
3. Social risk: We do not anticipate any social risk in this study.
4. Economic risk: There will be no cost to subjects during this study, neither will there by any remuneration.
5. Potential benefit of participating in the study
    a. to the individual subject and/or parent if any: None
    b. to the population from which the subject is drawn: TXA in this patient population is sporadic and varies widely from surgeon to surgeon. Providing a definitive answer regarding the safety and efficacy of TXA in this patient population would both unify the musculoskeletal oncology field in their use or abandonment of TXA,

and potentially improve oncologic patient care in a similar fashion than that seen with the use of TXA in arthroplasty.

c. to science, society, and humanity in general: A definitive answer regarding the safety and efficacy of TXA in this patient population would both unify the musculoskeletal oncology field in their use or abandonment of TXA

G. Location where study will be performed: This will be a multi-institutional study with the University of Kansas Medical Center being the coordinating site. We have interest from multiple institutions but they are awaiting our IRB approval. These include the University of Chicago, Oklahoma, St. Louis University, Cleveland Clinic, and MUSC, Iowa, Penn, and others. Recruitment of study participants will take place at the University of Kansas Medical Center and the University of Kansas Hospital Indian Creek Campus. Recruitment will also take place at participating institutions. Data will be collected for the primary and secondary endpoints from patients' electronic medical records and will be compiled electronically. The research subject's records will be stored electronically on a hard-drive in a passwordprotected and encrypted computer at the University of Kansas Medical Center **H. Collaboration (with another institution, if applicable):** see Item "I" below.

I. Single IRB Review for a Multi-site study (if applicable):

1. For which sites will KUMC serve as the IRB of record? Only Kanas University Medical Center. Participating institutions will work through their own IRBs for review and approval.
2. Indicate which study activities will occur at each site. If all study procedures will be identical across study sites, state this. Identical across sites.
3. Describe how you will assess the capacity of each site to perform the research (e.g., expertise, staffing, space, equipment, etc.) If applicable, include site evaluation tools in your IRB submission. All sites will have a fellowship trained orthopaedic oncologist who treats sarcomas regularly. They will all be at academic institutions with their own IRBs and experience in conducting clinical trials.
4. Describe how the lead investigators will ensure that all participating sites use the IRBapproved version of the protocol, consent, recruitment materials and other study documents. We will have mobile monthly phone conferences to discuss enrollment and issues related to the study. Further contact will be provided by Sharon Bradshaw, the orthopaedic department's research coordinator. Approved protocol documents will be sent by study coordinator/PI directly to participating sites' designated research team members. Any updated documents will be sent to all sites as soon as they are approved. Describe how the lead investigators will communicate with and disseminate new information to other sites (e.g., training meetings, regularly-scheduled conference calls, notifications, etc.) We will have mobile monthly phone conferences to discuss enrollment and issues related to the study. Sites not included on those conferences will be contacted directly by the PI (Kyle Sweeney) or study coordinator (Sharon Bradshaw).
5. Describe how the lead investigator will assess protocol compliance, unanticipated problems and adverse events at other sites. We will have mobile monthly phone conferences to discuss enrollment and issues related to the study. In addition, Sharon Bradshaw will be available to be contacted by other institution to answer questions regarding the protocol. I will be in contact with the other PIs at the monthly meeting.
6. Name the member of the KUMC study team who will be the point of contact to coordinate oversight and communication with the sites. Sharon Bradshaw

J. Community-Based Participatory Research (if applicable) 1.
Participants and the nature of their involvement: N/A

2. Cultural issues: We do not anticipate cultural or community attitudes to affect the research study. A certified interpreter will be utilized during the recruitment and consent process if needed.

3. Origin of the research question: The impetus and idea for this study came from the researchers alone.

4. Risks and Benefits: N/A

5. Study Description and Process: N/A

6. Return of results: The results will be published by the principle investigator and coinvestigators. There is not an explicit agreement between researchers and community participants about the research results.

7. Sustainability: N/A

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): Dr. Kyle Sweeney MD, Dr. Howard Rosenthal MD, Dr. Jacob Birlingmair MD
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Dr. Kyle Sweeney MD, Dr. Howard Rosenthal MD, Dr. Kimbery Templeton, MD
    b. Obtaining informed consent: Dr. Kyle Sweeney MD, Dr. Howard Rosenthal MD, Dr. Kimberly Templeton MD
    c. Providing on-going information to the study sponsor and the IRB: Dr. Kyle Sweeney MD, Dr. Jacob Birlingmair MD, Sharon Bradshaw
    d. Maintaining participant's research records: Dr. Kyle Sweeney MD, Dr. Jacob Birlingmair MD, Sharon Bradshaw
    e. Completing physical examination: Dr. Kyle Sweeney MD, Dr. Howard Rosenthal MD, Dr. Kimberly Templeton MD
    f. Taking vital signs, height, weight: Clinical support staff for participating surgeons
    g. Drawing / collecting laboratory specimens: Clinical support staff for participating surgeons
    h. Performing / conducting tests, procedures, interventions, questionnaires: Dr. Kyle Sweeney MD, Dr. Howard Rosenthal MD, Dr. Kimberly Templeton MD

i. Completing study data forms: Dr. Kyle Sweeney MD, Dr. Jacob Birlingmair MD, Dr. Howard Rosenthal MD, Dr. Kimberly Templeton MD

j. Managing study database: Dr. Kyle Sweeney MD, Dr. Jacob Birlingmair MD, Sharon Bradshaw

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. Please note that any study proposal with more than minimal risk must include a data and safety monitoring plan. Elements of the plan include:
    a. Persons/groups who will review the data (study team; independent safety monitor, data monitoring committee or formal DSMB) - Study team
        i. An independent safety monitor will be used. Dr. Brent Wise, MD is an orthopaedic surgeon familiar with the use of TXA and uninvolved with the study in any other capacity.

    b. Data/events that will be reviewed - Adverse events/complications arising in the participating patients.
    c. Frequency of review: Review will occur every 4 months routinely. Additionally, a review will be conducted if 5 separate adverse events are reported prior to the scheduled bi-annual review.
    d. Types of analyses to be performed – we will analyze the rate of complications (infections, PE, DVT) between the groups to make sure that we aren't getting statistically significant differences between groups
    e. Safety-related triggers that would cause the PI to stop or alter the study – If our analysis of complications reveals a statistically significant difference between groups, we will place the study on hold until an appropriate remedy can be reached. We will consult with the IRB before resuming the study. If no remedy can be determined the study will be permanently held
2. Describe how adverse events and unanticipated problems will be ascertained and handled. Explain exactly which type of problems will be considered serious and reported to the IRB. The reporting timeframe should also be detailed - Sites will report serious adverse events and unanticipated problems within 72 hours to coordinating center (KUMC). The independent monitor and Primary investigator will be made aware and the independent safety monitor will determine if a further review is necessary and/or further action needs to be taken.
3. Explain exactly what will happen if a patient experiences an adverse event or other problem (for example, will discontinue study participation) - Serious adverse events will be reviewed by the independent safety monitor, principal investigator, and treating surgeon where it will be determined if study participation should be continued or not.

III. Subject Participation

A. Recruitment:

Patients that present to participating surgeons' clinics that meet inclusion criteria and do not meet exclusion criteria will be recruited for this study. The treating surgeon will conduct all of the recruitment and consent aspects of this study in his or her clinic. If the treating surgeon deems a patient to be eligible for this study based on our inclusion and exclusion criteria then these patients will be asked to participate in this study in a

noncoercive manner. We will not construct any advertisements or flyers that attempt to recruit study subjects.

Attach a copy of the recruitment letter or introductory statement and describe planned use or distribution of the document. We will not use a recruitment letter for this study.

B. Screening Interview/questionnaire: N/A. We will not use interviews or questionnaires for screening. In order to be included in this study the subjects must meet set parameters (inclusion and exclusion criteria). Evaluation of whether patients can be included in this study will be based on chart review and patient history acquisition. This will be performed by participating surgeon.

C. Informed consent process and timing of obtaining of consent

1 Indicate who will give subjects detailed and comprehensive information about the study and obtain their written consent. The treating surgeon or designated coordinator will give subjects detailed and comprehensive information about the study and will obtain their written consent. The same standard principals that guide obtaining informed consent for their surgical procedure will be used.

2 Indicate how the consenting process will be structured to ensure independent and thoughtful decision-making, and what steps will be taken to avoid coercion and guarantee confidentiality. The same standard principals that guide obtaining informed consent for a surgical procedure will be used.

3 Indicate how, and by whom, it will be determined whether the subject is able to give informed consent, or whether their legal guardian will give informed consent. For subjects whose ability to give informed consent may be compromised by cognitive and/or decisional impairment (examples may include individuals with a psychiatric disorder, an organic impairment, a developmental disorder, or those suffering from a terminal illness, degenerative disease, severe physical handicap or dependence on drugs or alcohol), complete Appendix I. The same standard principals that guide obtaining informed consent for surgical procedures will be used. Patients unable to give informed consent will not be included in the study.

D. Alternatives to Participation: Statement of Alternatives: The only alternative to participating in this study is not to participate. All subjects have the right to withdraw from the study at any time. If you wish to be removed from this study, you can contact Dr. Kyle Sweeney.

E. Costs to Subjects: The laboratory tests/follow up visits that will occur during this study are standard as defined by the principle investigator regardless of whether the patient participates in the study. For example, a patient who chose to not participate in this study will undergo the same tests/labs/follow up appointments as a patient who decided to participate in this study. We do not anticipate any costs will be related solely to subjects participating in this study.

F. How new information will be conveyed to the study subject and how it will be documented: New information will be given to study subjects in writing.

G. Payment, including a prorated plan for payment: Subjects will not be paid or reimbursed for their participation in this study.

H. Payment for a research-related injury: If injury or illness is a direct result of participation in this study, immediate treatment will be provided as deemed appropriate by the principle investigator. However, the cost of that treatment will be billed to the individual or their insurance company. The patient will be aware that their insurance company may decide not to pay.

IV. Data Collection and Protection

1. **Data Management and Security:**
The principle investigator and co-investigators will have sole access to the study data. All data will be stored in the KUMC department network drive provided by Information Resources. An encrypted file location will be requested by contacting KUMC Information Security. Human subjects will be identifiable via their medical record number. No linking list will be maintained following data collection and final submission to an academic journal which will protect the identity and confidentiality of patients. Data will be stored on a password protected computer within the KUMC department drive and only utilized/viewed by the principle investigator and co-investigators. Data analysis conducted on a private computer will occur only using data that is void of personal identifiable information. Data will not be shared with individuals outside of KUMC. The individual accessing the data would like to preserve the data for a sufficient time to complete the collection, analysis, and final submission to an academic journal. It is anticipated that the list that links the subject's identity to the study data will be destroyed within 3 years of study completion.

A. Sample / Specimen Collection: N/A

B. Tissue Banking Considerations: N/A

C. Procedures to protect subject confidentiality: The risk of loss of confidentiality will be minimized by the fact that the data will be managed by the study investigators (who will have sole access to the data), and stored electronically on a hard-drive in a passwordprotected and encrypted computer at the University of Kansas Medical Center. The records will be kept using each patient's medical record number, age, and sex. No other identifiers will be used in this study.

D. Quality Assurance / Monitoring

1. Describe steps to be taken to assure that the data collected are accurate, consistent, complete and reliable. (source data verification, audits or self – assessment) Source data verification and self-audits will be performed. The protocol for the clinical trial will be spelled out for the participants. A discussion will be had between the PI at KUMC and the PI at the participating institution to ensure the protocol is understood.

V. Data Analysis and Reporting

A. Statistical and Data Analysis: Group differences in preoperative hemoglobin and hematocrit, transfusion requirements, drain output at 24 hours, difference in hemoglobin balance method, and changes in hemoglobin and hematocrit will be compared using pairwise Student T-test analysis. Pairwise T-tests between each of the groups (for continuous

variables) and Chi squared analysis (for categorical variables) will be used to determine if a statistically significant difference exists between the groups in terms of the patient specific factors that are also collected and analyzed (age, sex, smoking status, BMI, operative time, length of stay, presence of coagulopathy, specific anticoagulation regimen should it differ from study protocol, size of resection, depth of resection, location of tumor, pathologic diagnosis, stage of disease).

B. Outcome: We expect the results to be similar to the TXA arthroplasty studies/literature with regards to decreased perioperative blood loss and decreased transfusion rates. There are not necessarily any criteria for success or failure. The results of this study will help provide a definitive answer regarding the safety and efficacy of TXA in oncologic patients. This will help unify the musculoskeletal oncology field in their use or abandonment of TXA.

C. Study results to participants: The study results/conclusions will not be given to subjects unless they are specifically asked for at future scheduled outpatient clinic visits. Once the proposed study is completed a conversation with subjects can occur on an outpatient basis at their routine scheduled clinic visits regarding our results and conclusions if desired. The subjects reserve the right to know what conclusions were drawn from the study they directly participated in. In addition, we plan to publish a manuscript with our results/conclusions after completion of the study which can be sought after if desired.

D. Publication Plan: The results will be published by the principal investigator and coinvestigators within the orthopaedic surgery department. Results will be submitted for publishing within 6 months of data analysis. The principal investigator and co-investigators within the department of orthopaedic surgery will be primarily involved in the compilation of the study results.

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APPENDIX I: VULNERABLE POPULATIONS

I. The recruitment plan will not include any of the groups noted below.

II. **Cognitively or decisionally impaired individuals**: N/A. Cognitively or decisionally impaired individuals will be excluded from this study.

III. **Children**: N/A. Children will be excluded from this study.

IV. **Pregnant women:** N/A. Pregnant women will be excluded from this study.

V. **Prisoners:** N/A. Prisoners will be excluded from this study.

VI. **Students and/or Employees**: N/A. Students and/or Employees at KUMC will be excluded from this study.