PREVENT CLOT Protocol and Statistical Analysis Plan
February 1, 2023

This document includes the following:

Major Extremity Trauma Research Consortium (METRC):

PREVENTion of Clot in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

Sponsored by: PCORI

Contract Number:
PCS-1511-32745

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This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from METRC (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

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List of General Abbreviations/Terminology

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DVT	Deep Venous Thrombosis
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LMWH	Low Molecular Weight Heparin
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
OHRP	Office for Human Research Protections
PE	Pulmonary Embolism
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAB	Stakeholder Advisory Board
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
VTE	Venous thromboembolism

PROTOCOL SUMMARY

Title: Prevention of Clots in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

Sponsor: Patient Centered Outcomes Research Institute (PCORI)

Type of study: Randomized Pragmatic Trial

Objective: *Is Low Molecular Weight Heparin (LMWH) (Enoxaparin) or Aspirin the better medicine to use for preventing death and clinically important blood clots in the lungs in patients who sustain trauma?*

We aim to make the following comparisons between aspirin and the LMWH:

Specific Aim 1: The proportion of patients who sustain death due to PE or VTE prophylaxis after orthopaedic trauma treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 1: The rate will be non-inferior in the aspirin group.)

Specific Aim 2: The proportion of patients who sustain clinically important pulmonary embolism (PE) after orthopaedic trauma treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 2: The rate will be non-inferior in the aspirin group.)

Specific Aim 3: The proportion of complications (clinically significant bleeding or infection events) in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 3: The rate of complications will be superior (i.e., lower) in the aspirin group)

We will pursue the following secondary aims:

Secondary Aim #1: Assess satisfaction with care in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 4: Satisfaction will be superior in the aspirin group.)

Secondary Aim #2: Estimate out of pocket patient costs in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 5: Out of pocket costs will be lower in the aspirin group.)

Secondary Aim #3: Examine the proportion of minor clot events that are less important to patients (clots in the proximal legs, incidental PE) in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 6: The rate will be non-inferior in the aspirin group.)

Secondary Aim #4: Estimate adherence with treatment among orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 7: Adherence will be higher in the aspirin group.)

Study duration: 5 years: 1 year of planning, 3.5 years of recruitment and follow-up, 0.5 years of analysis and dissemination of study results

Sample size: 12,200 (6,100 per arm (2) arms)

Number of study sites: up to 30

Study population: Orthopaedic trauma patients, ages 18 and over

Inclusion criteria: Trauma patients who are at increased risk of blood clots from their traumatic orthopaedic injury and are therefore currently treated with blood clot prevention medicine, including operatively treated extremity injuries and all pelvis or acetabulum fractures (operative and non-operative)

Exclusion criteria: Patients who do not require prophylactic blood thinners as standard of practice; Patients who are already on long term blood thinners (other than low-dose aspirin or platelet inhibitors such as Plavix or Aggrenox) or who require therapeutic (as opposed to prophylactic) blood thinners for an acute issue such as a blood clot in the last 6 months); Patients who cannot receive either of the study medications due to an allergy (history of heparain induced thrombocytopenia, allergy to aspirin, or NSAIDs) or other medical contraindication to blood thinners; Patients who are on higher dose aspirin (>81 mg once a day or higher) for medical reasons or who will be treated with higher dose aspirin; Patients with underlying chronic clotting disorders (i.e. Factor V Leiden, hyperhomocystinuria, Protein C and S deficiency) that require full dose anticoagulation or are a contraindication to VTE chemoprophylaxis; End stage renal disease, impaired creatinine clearance <30 ml/min at time of randomization (note: creatinine clearance does not need to be documented if prescribing physician would order medication without test as SOC); Pregnant or lactating patients; Patients contraindicated for any reason for either medicine; Prisoners; Patients who do not speak either English or Spanish. Patients may be excluded for other reasons at the discretion of the treating physician; the reason for exclusion must be documented on the screening form. Patients must be enrolled prior to receiving more than 2 doses of LMWH or Aspirin for initial prophylaxis.

Outcome measure: Death, pulmonary embolism, orthopaedic complication requiring surgery, satisfaction, out of pocket patient costs, minor clotting events.

Statistical analysis: Non-inferiority intent to treat analysis for study primary aim.

Randomization: Block randomization at the center level.

Safety monitoring: The Medical Monitor is responsible for monitoring serious adverse events (SAEs) as the study progresses to ensure patient safety. The DSMB will review all safety data at its scheduled meetings. The Medical Monitor may convene a meeting of the DSMB to evaluate any SAEs that he/she determines require immediate attention.

Data Safety and Monitoring Board (DSMB): The DSMB is an independent body responsible for evaluating recruitment, safety and outcome data. The DSMB has the authority to stop the study based on its findings.

1. KEY ROLES

Protocol Committee- Responsible for developing a detailed study protocol, provides oversight on study progress and acts to correct deficiencies in the conduct of the study. This committee also drafts the main publications related to the study.

Steering Committee- The Science Committee of the METRC Consortium will review the composition of the protocol committee and provide scientific review of the study protocol, with the purpose of presenting the protocol to the Consortium Steering Committee for approval. Additionally, the study will have a Steering Committee comprised of the study investigators, an orthopaedic and general surgery investigator from each participating center, 2-3 experts on clot prevention, and the patient and consumer stakeholders who comprise our Stakeholder Advisory Committee.

METRC Coordinating Center- Responsible for maintaining all study documentation, developing and maintaining the master IRB application and consent, circulating any changes to study documents including protocols, case report forms, and IRB materials to each participating center, providing daily oversight and management of study implementation, providing payment to sites for patients enrolled, performing site monitoring, data quality control and analysis of study results.

Clinical Sites- Responsible for the conduct of clinical studies including patient enrollment, performing study procedures, data collection and conducting study follow-up visits.

Clinical Outcome Adjudication Committee (COAC)- This committee will be responsible for developing the timely medical review and adjudication of trial-specific endpoints utilizing trial-specific definitions; engages other reviewers as needed and in accordance with the COAC Policy; and reports adjudication results to the trial-specific Protocol Committee.

Publication Committee- Responsible for reviewing manuscripts prior to journal submission and reviewing presentations prior to presentation; for mediating and settling disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations; for preparing and maintaining a list of concepts for publications and preparing and maintaining a list of approved METRC publications, which shows the status of each manuscript from initiation through publication.

DSMB- Independent Data and Safety Monitoring Board (DSMB) convened for this project, responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality.

Medical Monitor- Responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety

goals and objectives. This is achieved through the review of safety reports; resolving safety issues; and interacting with Principal Investigators.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Importance of Blood Clots and Blood Clot Prevention Medicines. Preventing venous thromboembolism (VTE) in the legs or lungs is a major unsolved problem in modern medicine. Each year, in the United States alone, blood clots are estimated to affect 300,000 – 600,000 patients.[1] These events may have important consequences for patients. VTE can include both deep venous thrombosis (DVT) and pulmonary embolism (PE). Even minor blood clots require a minimum of 6 months of medication, often with frequent blood tests, and increased risk of medication-related bleeding. At the most severe end, PEs are thought to account for 60,000–100,000 deaths per year in the United States.[2]

Patients who sustain trauma are well known to be at an increased risk for blood clots throughout their body, including fatal PE's.[3] There are 6 million fractures treated each year in the United States alone and 2.3 million patients are admitted each year after trauma.[4-6] Hip and femur fractures specifically are among the most common fractures and are associated with a particularly high risk of blood clots.[7,8] Current guidelines indicate that most orthopaedic trauma patients should be given medication to reduce the risk of blood clots.[9,10] Despite the common nature of these injuries and the potential devastating impact that blood clots can have on patients' lives, we currently do not know the best prophylactic regimen for these patients.

The ideal clot prevention medication for orthopaedic trauma patients would prevent death from PE and other consequences of blood clots while also limiting complications from the medication, such as bleeding from surgical wounds and other sources.[11] A blood clot resulting in death is obviously a devastating outcome for a patient and their family; however, other complications from clot prevention medications are not insignificant and may require surgery and have a major impact on the lives of patients, including, permanent disability in some cases.[12,13] Even under ideal conditions the medications used to reduce clots cannot completely eliminate the chance of blood clots and in some instances may lead to death themselves.[12-14]

Low molecular weight heparins (LMWH) are medications that have been utilized to lower the rates of proximal deep venous thrombosis in trauma patients since the 1990's and are currently the preferred agents across many guidelines, including those from the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma.[9,10] The case for the use of LMWH in this trial is relatively straight forward as it is the current treatment recommended by these guidelines and is commonly used in most north American trauma centers. While these guidelines are well intentioned, they are based on limited evidence regarding fracture patients, and do not incorporate patient preferences. There is good evidence that LMWH's are effective at limiting DVT, particularly asymptomatic DVT found on screening studies as a part of a research protocol.[3,15,16] However feedback from patients indicates that they are more concerned with PE's

that might cause death or clot prevention medication-related complications that require surgical treatment, rather than blood clots in the leg that are often asymptomatic or of minimal clinical consequence. This was confirmed by our own pilot research (conducted under a separate IRB). We interviewed 232 orthopaedic trauma patients and found that patients value the prevention of death and avoidance of surgical complications much more than other issues related to clot prevention medications.[17]

Despite the widespread use of LMWH to reduce PE after orthopaedic trauma, a recent Cochrane review actually showed limited evidence that LMWH affects the rate of PE or mortality in trauma patients,[3] and there is concern that there is potential for higher rates of bleeding into critical organs and surgical wounds associated with LMWH compared to other clot prevention medications in non-trauma related orthopaedic surgery.[18-20] This has led many to wonder if there is another alternative to clot prevention than LMWH for trauma patients.

Aspirin is another commonly used clot prevention medication, which may have a similar efficacy at preventing both PE and death in lower extremity injuries.[21] For both hip fracture and lower extremity arthroplasty surgery, substantial reductions in surgical wound hematomas have been noted with aspirin.[22] In addition, after lower extremity arthroplasty, LMWH has been associated with higher all-cause mortality as compared to the use of aspirin.[12] Although there are certainly strong advocates for the use of aspirin in orthopaedic trauma patients and some solid studies in arthroplasty supporting its use,[21,23-25] the efficacy of ASA has not been characterized relative to LMWH in this population yet.

No Data for Guidelines: A recent study on this topic by the Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlighted a knowledge gap surrounding clot prevention in orthopaedic trauma patients and concluded that there is "wide variability in practice patterns, poor scientific support for various therapeutic regimens" and guidelines are needed to "improve patient care."[26] As demonstrated by this study, there is a clear need for guidelines on clot prevention in trauma patients,[26] but there are no large high quality trials upon which to base these guidelines, as described by the Cochrane review on this topic.[3] Most of the existing guidelines make recommendations that are based on either arthroplasty patients (who are a poor surrogate for trauma patients), or an older subset of hip fracture patients, limiting the applicability to the vast majority of patients who fundamentally differ from either of these groups. Unfortunately this knowledge gap leaves clinicians and patients to make decisions about which VTE prophylaxis to use in this large patient population without adequate data to guide them.

2.2 Rationale

The best medication to reduce the risk of fatal PE for orthopaedic trauma patients who are admitted to a hospital after trauma each year in the United States is still unknown, creating decisional uncertainty for both patients and clinicians.[26] Recent meta-analysis on medications to prevent blood clots after major lower extremity surgery included no studies involving high energy trauma and only two small studies on hip fractures, concluding that "the rarity of

pulmonary embolism made meaningful comparisons between aspirin and anticoagulation impossible …"[22] The rarity of PE requires a large trial to answer this question and none exist to date. Similarly, a recent Cochrane review on this topic in trauma patients did not address the use of aspirin for clot prevention presumably due to a complete lack of data on the topic.[3]

There is little data on how commonly used medications like LMWH perform in trauma patients relative to enteral aspirin, likely because of the large patient sample size needed to address this issue. Moreover, the currently limited research in this topic has focused more on clinically insignificant DVTs, and have not been powered to address the outcomes most important to patients and clinicians, including bleeding complications and fatal PE.[3,22]

In addition to the lack of guidelines to support clinical decision making, there is a lack of evidence on how the choice of chemoprophylaxis following orthopaedic trauma affects patient satisfaction. Factors that are important to patients such as the need for the medicine to be injected or the out of pocket costs have been almost totally ignored to date.[3,22,26,27]

To address these critical gaps in the evidence we have designed a large, pragmatic, multicenter randomized clinical trial. This trial will provide definitive evidence for decision makers on whether aspirin is as effective as LMWH at preventing death and symptomatic PE, while potentially resulting in significantly fewer medication associated complications. The study fills several large and critical knowledge gaps of great interest to patients and clinicians and has great potential to improve the quality of evidence available for patients and other stakeholders to make informed decisions.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks The risks associated with participation in this study are primarily the risks that are associated with each of the study drugs.

Patients randomized to the LMWH arm would have no drug-related risk over and above the risk they would experience as standard of care. These risks include bruising or infection at the site of injection and allergic reaction, ranging from hives and itching to difficulty breathing or throat swelling. Some participants may experience Heparin Induced Thrombocytopenia, which results in a reduced number of platelets and hypercoagulability. Risks associated with the LMWH arm also include bleeding complications, which could require transfusion or operation, and kidney damage.

Patients randomized to the aspirin arm would have no drug-related risk over and above the risk they would experience as using aspirin for blood clot prevention. These risks include the potential to experience the risks associated with aspirin, including possible risk of inflammation or ulceration of the stomach, allergic reaction (ranging from hives and itching to difficulty breathing or throat swelling), ringing of the ears, and worsening asthma. Additionally, some patients have increased risk of bleeding and of kidney damage.

There is potential that patients in the aspirin arm will be at lower or higher risk relative to the patients in the LMWH arm just as there is a risk for patients in the LMWH arm to have better or worse outcomes than those in the aspirin arm. The trial is designed to assess this potential difference in risk.

A DSMB for the study will closely monitor event reporting, and should differential risks or benefits be identified, will consider stopping the study.

In this study, as with many others, there is a potential risk of breach of confidentiality, although the study team will make all reasonable efforts to mitigate this risk.

2.3.2 Potential Benefits It is not clear that one drug treatment will provide any benefit over another. Patient participants will receive $20 as compensation for time and effort returning for the 3-month study visit.

3. STUDY OBJECTIVES & OUTCOMES

3.1 Primary Objective:

We aim to make the following comparisons between aspirin and the LMWH:

Specific Aim 1: The proportion of patients who sustain death due to PE or VTE prophylaxis after orthopaedic trauma treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 1: The rate will be non-inferior in the aspirin group.)

Specific Aim 2: The proportion of patients who sustain clinically important pulmonary embolism (PE) after orthopaedic trauma treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 2: The rate will be non-inferior in the aspirin group.)

Specific Aim 3: The proportion of complications (clinically significant bleeding or infection events) in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 3: The rate of complications will be superior (i.e., lower) in the aspirin group)

3.2 Secondary Objectives:

We will pursue the following secondary aims:

Secondary Aim #1: Assess satisfaction with care in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 4: Satisfaction will be superior in the aspirin group.)

Secondary Aim #2: Estimate out of pocket patient costs in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 5: Out of pocket costs will be lower in the aspirin group.)

Secondary Aim #3: Examine the proportion of minor clot events that are less important to patients (clots in the proximal legs, incidental PE) in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 6: The rate will be non-inferior in the aspirin group.)

Secondary Aim #4: Estimate adherence with treatment among orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 7: Adherence will be higher in the aspirin group.)

3.3 Study Outcomes

To meet study objectives, the following clinical outcomes will be assessed:

- Death: The primary outcome for this study is death due to pulmonary embolism or VTE prophylaxis. Cause of death will be recorded in addition to an assignment of certainty of the attribution. Cause of death will be categorized as "Certain" (e.g. there is an autopsy or operative note indicating cause of death), "Highly Likely" (e.g. clinical information available indicating likely cause of death, but no autopsy or corroborating data available), or "Uncertain" (e.g. participant did not die in a clinical setting and only data available to support assignment of causality is based on the report on non-clinical family or friends). From this information, we will be able to analyze data on all cause mortality in addition to deaths attributable to pulmonary embolism or VTE prophylaxis.
- Clinically important pulmonary embolism (massive, submassive, or other symptomatic events (found by test for PE)[28])
- Complications, including the following:
    - Wound drainage, hematoma or seroma of an orthopaedic injury requiring reoperation
    - Diagnosis of deep surgical site infection of an orthopaedic injury requiring operation.
    - Diagnosis of a deep surgical site infection of an orthopaedic injury, not requiring operation
    - Clinically overt bleed with a > 2g/dL drop in Hb or requiring > 2U transfusion[29,30]
    - GI bleed
    - Other bleeding complications following study enrollment and receipt of first dose of study medication requiring procedure
    - Lower extremity DVT distal to knee
    - Lower extremity or pelvic DVT proximal to knee
    - Other DVT
    - Studies ordered related to concerns for bleeding or VTE event

- Negative VTE study (type and date)
- Negative study for bleeding concern (type and date)

The following outcomes will be assessed to address the study's secondary aims:

- Patient satisfaction will be measured using a validated questionnaire called the Short Form Patient Satisfaction Questionnaire (PSQ-18).[31,32] The PSQ was originally developed by Ware and colleagues,[33] included 80 items, and was successfully used as part of the RAND Health Insurance Experiment and Medical Outcomes Study.[34] The PSQ-18 measures all 6 sub-domains (technical quality, interpersonal manner, communication, financial aspects of care, time spent with doctor, and accessibility) as the longer form, as well as a single global satisfaction domain.[35] The domains measured by the PSQ-18 correlate at 0.8 or better with domains measured using the long form PSQ.[32] The PSQ will be revised to be made specific to the treatments under study. Two questions specific to orthopaedic trauma care using the same format and structure as the rest of the instrument will be added to measure satisfaction with treatment for this study.
- Direct out of pocket medication cost to the patients related to the blood clot medicines as reported at the final follow up visit
- Blood clots in the legs or lungs that are not associated with a PE and discovered through routine, standard of care procedures. No additional tests (venography) will be performed to screen for these events, as blood clots that are causing no symptoms are likely of no clinical consequence and are not important to patients. Furthermore, additional tests could potentially decrease the willingness of patients to participate in the trial. The outcome will be driven only those blood clots that are discovered as part of the normal clinical care at each trauma center.
- Adherence to treatment will be defined as percent of doses taken compared to those prescribed, assessed while in-patient and at the final follow up visit.

4. STUDY OVERVIEW

The proposed study is a pragmatic multi-center, prospective, randomized trial of 30 mg of subcutaneous low molecular weight heparin/enoxaparin (LMWH) administered twice daily versus 81 mg of enteral aspirin (ASA) taken twice daily in orthopaedic trauma patients. Treatment will be initiated during the initial hospitalization for injury, and will continue for the duration of time the patient is prescribed prophylactic clot prevention medication, per the standard of care at the treating facility. Patients will be followed for 3 months (plus or minus 1 month) following date of admission to the trauma center to assess for death, rehospitalization, or complication which occurred between discharge and follow up. At this time, satisfaction, adherence and out of pocket costs will also be reported.

5. STUDY POPULATION

5.1 Description of the Study Population

Approximately 12,200 participants (6,100 per treatment arm) will be enrolled from participating METRC centers over a 42 month period. Participants will be recruited as soon as the decision to place them on prophylactic clot prevention medication is made at the initial hospitalization for their injuries. Consenting procedures are described in detail in Section 6 of this protocol.

5.1.1 Participant Inclusion Criteria

We will include patients ages 18 years and over and anticipate that participants' demographics will be representative of the US trauma population in terms of gender, race, and ethnicity due to our multicenter design. The study will include trauma patients who are at increased risk of blood clots from their orthopaedic traumatic injury (operatively treated extremity injuries and all pelvis or acetabulum fractures that are treated either operatively or non operatively) and for whom a prophylactic blood thinner regimen would be standard of care at their institution. To ensure that our population is representative of typical trauma patients and to enhance the generalizability of our findings, the participants may have other orthopaedic and non-orthopaedic injuries and still be included.

5.1.2 Participant Exclusion criteria

Patients who do not require prophylactic blood thinners as standard of practice; Patients who are already on long term blood thinners (other than low-dose aspirin or platelet inhibitors such as Plavix or Aggrenox) or who require therapeutic (as opposed to prophylactic) blood thinners for an acute issue such as a blood clot in the last 6 months); Patients who cannot receive either of the study medications due to an allergy (history of heparain induced thrombocytopenia, allergy to aspirin, or NSAIDs) or other medical contraindication to blood thinners; Patients who are on higher dose aspirin (>81 mg once a day or higher) for medical reasons or who will be treated with higher dose aspirin; Patients with underlying chronic clotting disorders (i.e. Factor V Leiden, hyperhomocystinuria, Protein C and S deficiency) that require full dose anticoagulation or are a contraindication to VTE chemoprophylaxis; End stage renal disease, impaired creatinine clearance <30 ml/min at time of randomization (note: creatinine clearance does not need to be documented if prescribing physician would order medication without test as SOC); Pregnant or lactating patients; Patients contraindicated for any reason for either medicine; Prisoners; Patients who do not speak either English or Spanish. Patients may be excluded for other reasons at the discretion of the treating physician; the reason for exclusion must be documented on the screening form. Patients must be enrolled prior to receiving more than 2 doses of LMWH or Aspirin for initial prophylaxis.

5.1.3 Co-Enrollment Guidelines

Patients may be co-enrolled into this and other studies, depending on the practices of the local IRB. Co-enrollment must be documented, and event reporting for either study must be reported for both projects.

6. STUDY PROCEDURES

6.1 Screening and Enrollment

6.1.1 Screening

All patients 18 years of age and older with an orthopaedic injury and for whom prophylactic clot prevention medication is indicated will be screened for eligibility at each site by the local Research Coordinator in close collaboration with the surgeon investigators. In this study, it will be important to enroll patients soon after admission to ensure study medication can commence in a timely manner.

A partial HIPAA Waiver will be requested for the purposes of screening for enrollment. The study team will discuss all participants meeting inclusion criteria, and complete and submit a screening case report form (CRF) on every potentially eligible participant. The medical record will be reviewed to assess for exclusion criteria, and the results will be entered into REDCap, the METRC electronic data capture system, in order to document screen failures. The study PI will be available via text or email to answer questions regarding study eligibility. This service will be active during regular east and west coast business hours. When the study PI is not available, this coverage will be provided by a designated co-investigator. Contact information for the PI and alternate contact is available in Appendix A.

6.1.2 Consent and Enrollment

Once eligibility has been confirmed, the informed consent process will be completed by the Research Coordinator and/or a clinician certified to participate in this study. Eligible study participants or their legally authorized representative (LAR) will be approached as soon as they are able to give consent, and may be enrolled in the study through the time that the first two doses of anticoagulation therapy are administered; i.e. they may receive 2 doses of SOC (as defined by the center) therapy prior to randomization and initiation of the study-directed medication. Individual sites will develop local procedures that will ensure these requirements can be met. Patients and their families will be provided with a pamphlet describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate. If a patient is unable to consent before 2 doses of SOC anticoagulation therapy are administered and there is no LAR available, the patient will not be eligible for study participation and will be recorded as such. Consent will be obtained in accordance with principles of GCP and ICH guidelines.

A prototype consent has been prepared for this study and is attached in Appendix C. Individual sites may add material but may not delete material thought to be necessary for informed consent. Clinical sites may reformat and reword information to conform to their local requirements. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the signed consent forms will be given to the patient, and this fact will be documented in the patient's record.

All study materials will be provided in English and/or Spanish as appropriate.

Following completion of informed consent, the participant information will be entered into REDCap where a study number will be assigned, final eligibility criteria confirmed, and the participant will be randomized to a treatment group.

6.1.3 Assessing Capacity to Consent and Consenting a Proxy Respondent

The research staff will endeavor to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol. After introducing the study and reviewing the consent form, the research coordinator will pose several questions assessing the participant's comprehension of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation. The Research Coordinator will ask the questions and determine the appropriateness of the responses. If the Research Coordinator is at all unsure about the patient's ability to consent s/he will consult with the study site PI.

By virtue of the types of injuries studied (resulting from high energy mechanisms such as high speed motor vehicle crashes, high falls, and blast injuries) it is expected that we will have patients with an associated traumatic brain injury which may render them unable to provide consent for the study. Other patients may remain intubated for some time due to lung issues or other reasons related to their trauma. It will be important not to exclude these patients from the study, as it would significantly reduce our ability to produce generalizable knowledge. These patients are at no greater risk of adverse consequences by virtue of their participation in the study, and should be given the same opportunity to participate.

A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if one of the following is true:

- The patient is unresponsive or intubated (and likely to remain unresponsive or intubated during the enrollment window for the study).
- The patient cannot adequately answer at least 2 questions regarding study participation or it is determined that the patient's level of cognition is not likely to change before study medication can be initiated.

The choice of LAR will follow standard procedures and be any of the following: Legal guardian, Proxy (health care agent) named in an advance directive or durable power of attorney for health care; or Family member or other surrogate identified by the state law on health care decisions.

Guidance will be provided to assist the LAR in making the consent decision. They will be advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values and a willingness to administer the study medication, if the patient is still unable to consent at the time of discharge. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in

mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

Recognizing that consent is an ongoing process, the study team will continue to assess the participant for their ability to provide consent, and at the earliest possible time, will obtain informed consent from the patient him or herself. Similarly, any participant may withdraw consent at any time during participation in this study.

6.1.4 Informed Consent Process or Assent (for a minor)

N/A

6.2 Baseline Data Collection

Once consent is obtained, baseline data regarding participant characteristics, injury characteristics, fracture classification and medical history/co-morbidities will be collected and entered into the METRC custom version of the REDCap data collection system. Characteristics about hospital course and treatment received will also be collected. A brief interview will be conducted with the participant or his/her surrogate.

6.2.1 Medical Record Review

For all enrolled participants, data related to the index hospitalization will be collected. This will include a daily check of the medication administration record to ensure that the patient is receiving the study drug to which he/she was assigned and to document adherence. If treatment is stopped, held or changed the research team member will either identify the reason for change from the chart or by asking the primary team if the reason is not documented. Other data to be collected includes orthopaedic and other injury characteristics, admission labs, and complications, including a fatal bleed, >= 2 g/dL drop in hemoglobin, reoperation for hematoma evacuation or surgical site infection, other clinically significant bleeding or infectious complication, VTE, PE, and any imaging studies (and results) conducted for bleeding or VTE concerns. Information on the administration of a limited number of concomitant medications with known potential for bleeding side effects will also be collected, including Plavix, or other platelet inhibitors, aspirin, NSAIDs (e.g. toradol, ibuprofen), and any administration of a full dose of anticoagulation medication, as well as the reason, will be recorded.

6.2.2 Clinical Assessment

No additional clinical assessments will be conducted as part of this study.

6.3.3 Participant Interview

Participants, or their proxies, will complete a brief baseline data, including age, race, history of tobacco, medical history, including history of VTE, peptic ulcer, DM, or cancer, or if they are immunosuppressed, in addition to use of home OCP/estrogen, Plavix, or daily aspirin.

6.3 Participant Follow up and Data Collection

6.3.1 Follow-up Visit Schedule

Participants will return for a regularly scheduled standard of care follow-up visit at 3 months post admission. Each visit will have an interval of time surrounding the ideal date for the visit during which the visit may be completed and the data included in the trial database. This interval is approximately 4 weeks before or after the ideal date for the visit, which is the exact anniversary from the time of the admission.

At the time of the follow up visit, participants will be interviewed by the Research Coordinator to assess for the occurrence of any clinical outcomes, including VTE events or complications secondary to treatment since their hospitalization. For each event identified, the participant will fill out a release of information form that will allow the research staff to obtain records related to the event, if they occurred outside the index facility. Additionally, the medical record will be carefully reviewed to assess for any complications treated at the index facility, including in the clinic, ED, or resulting in a rehospitalization.

Participants who do not return to the study site will complete the same questions either by phone or an email link to the survey.

Attempts will be made to obtain medical records or autopsy reports for all participants who are discovered to be deceased at the time of the follow up visit. If the participant died at home, family members will be asked to provide a cause of death, if known. A search of the National Death Index will be conducted annually for all participants who cannot be found. This search will take place at the local site level. No attempts will be made to follow up with family, and the deaths will be recorded as “unknown” cause.

6.3.2 Retention

Every effort will be made to retain participants in the study. The study participants will receive an honorarium in recognition of their time and effort. $20 will be given for completing the **3** month visit in appreciation for their time and effort. Participants who complete follow-up activities by phone or email will be given $20 for competing the interview. We will also keep participants engaged through use of study updates on the study webpage and distribution of follow-up reminders, which can include mailings and e-mails.

7. STUDY TREATMENTS

Patients meeting inclusion/exclusion criteria will be prospectively randomized to one of two treatment arms using the REDCap Database randomization tool embedded. Block randomization with variable block sizes will be used.

7.1 Study Treatments

7.1.1 Description of treatment

Study Treatment 1: LMWH is currently an accepted medication used to prevent blood clots after trauma, and and its is supported by existing guidelines so it is already in widespread use through the United States.[9,10] Enoxaparin is available from multiple manufacturers; local site purchasing will determine the product received by the patient. Clear guidelines already exist regarding dosing in very obese patients as well as in patients with renal disease.[36,37] The LMWH intervention is expected to be 30 mg enoxaparin SC twice a day which is already standard in many trauma hospitals. The protocol for this pragmatic trial will allow for variations in dosing, per the standard of care at sites, as needed for patients who are very obese or exhibit renal dysfunction. These variances will be recorded to allow them to be identified in the data.

Study Treatment 2: Aspirin is currently regarded as an accepted medication to prevent blood clots after orthopaedic surgery, is supported by existing guidelines[38] and is already in widespread use in the United States. Aspirin is less commonly used in trauma although it has gained significant popularity in the orthopaedic arthroplasty (joint replacement) domain.[22,23,27] Aspirin was chosen as the comparative intervention because it is thought to have an excellent complication profile (low rates of bleeding and chronic wound drainage) and still to be effective in preventing blood clots in the lung, although these data are in joint replacement patients.[22,23,27,38] Aspirin works by effecting platelets irreversibly and this effect typically lasts 7 days, which is a potentially important difference from the shorter acting LMWH. The advantage of a shorter acting medication is that the effect can be turned off easily when the patient needs additional surgery or if a contraindication for bleeding develops. A down side is that missed doses with LMWH quickly place the patient with no blood clot prevention. Aspirin is typically continued even when surgeries are performed so the fact that aspirin cannot be “reversed” is likely not important in this domain, but the importance of this effect in trauma patients is unknown.

The dose of aspirin for this study is not obvious as several reported doses have been used successfully. Options include 81 mg once a day, 81 mg twice a day, 180 mg once a day, 325 mg once a day, and 325 mg twice a day. The desired effect of reducing the risk of clots is thought to occur at the 81 mg dose once a day and many joint replacement surgeons use this dose to prevent blood clots.[39] Anti-inflammatory effects are thought to become more pronounced as the dose increases and some of the original joint replacement studies used 325 mg twice a day. We believe that lower doses may be desirable in trauma as it likely reduces the chance of bleeding from other traumatic injuries and it is not necessarily desirable to have the anti-inflammatory effects of higher doses, as anti-inflammatory medicines have been linked to delayed bone healing

in animal models.[40] We therefore have chosen 81 mg twice a day as it represents a dose towards the lower end of the dosing spectrum and gives twice a day dosing, similar to LMWH, decreasing the chance of patients missing a dose for the whole day. Further, a study of geriatric hip fractures,[21] which is as close to our population as has been studied for this question, successfully used 160 mg once a day.

7.1.2 Investigational Drug Status

Both study treatments are FDA approved medications that are commonly used for the indication proposed in this application; however only LMWH has this listed as an approved indication in its product labelling. ASA for this indication is "off label" for use as DVT prophylaxis. In accordance with 21 CFR 312.2, this study meets IND Exemption requirements. An application for an IND exemption was approved by the FDA for the proposed indications outlined in this protocol. The intention of the protocol is not to support a new indication for use or significant change in labeling of the drugs; is not intended to support a change in advertising for the drugs; will not test a new route of administration or dosage of the drug, nor is it being used in a new clinical population; and the study will be conducted with informed consent and in compliance with 21 CFR 312.7 regarding promotion and sale of drugs. Patients in the study will be actively monitored for any adverse reactions.

7.2 Assessment of Participant Adherence with Study Agent(s)/Intervention(s)

Adherence to study medications and out of pocket costs will be assessed at the 3 month follow up visit, including assessing for any potential occurrence of treatment crossover.

If participants do not return for the 3 month study visit, they will be contacted by the study research coordinator by phone, mail and/or email. The participant will be asked to return to the clinic for a follow-up appointment. If the participant is unwilling to return, follow up information will be collected by phone or via an email survey assessing for adherence and study outcomes.

7.3 Precautionary and Prohibited Medications and Procedures

In this trial, participants will be randomized to receive either LMWH or aspirin. Participants in this study may not receive any other full dose medication as prophylaxis for anticoagulation or as treatment for a VTE even, nor may they receive additional dosages of aspirin above 81 mg daily. There are no other prohibitions regarding medications management, and participants will be treated according to the local standard of care. Data on specific concomitant medications will be collected (See Section 6.2.1). Should it be determined that the medication the participant was randomized to is no longer clinically appropriate, the study medication will be stopped, the research team will record the reason for medication discontinuation, and the participant will continue to be followed through the 3 month follow up.

7.4 Rescue Medications

Any need for rescue medication resulting from a drug overdose or sensitivity will be handled per the standard of care at the treating institution or where the patient seeks care.

8. ASSESSMENT OF SAFETY

The study will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. The approach to defining and reporting events is based on the 2009 FDA Guidance for Clinical Investigators, Sponsors, and IRBs on adverse event reporting to IRBs (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf)

The medical monitor (MM) is responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of Serious Adverse Event reports; resolving safety issues; and interacting with Principal Investigators.
Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.1 Definitions

8.1.1 Adverse event

Any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject's participation in the study, whether or not considered related to the subject's participation. Several adverse events, or complications, will be collected as primary and secondary outcomes of the study. The most severe of these events include: (1) Death, (2) Fatal bleeding into a critical organ (retroperitoneal, intracranial, intraocular, intraspinal); (3) Significant/massive PE central pulmonary embolism with resulting heart strain (PE); (4) Wound drainage or hematoma requiring reoperation; (5) Wound drainage, bleeding or hematoma that does not require reoperation; (6) Bleeding event that requires intervention (e.g. chest tube, interventional radiology embolization); (7) Surgical Site Infection requiring reoperation; (7/8) Surgical site infection that does no lead to reoperation but requiring antibiotic treatment; (9) Greater that 2 mg/dL drop in hemoglobin within 24 hrs; and (10) GI Bleed. These and other complications common in the trauma population will be reviewed in aggregate twice annually by the DSMB to assess for differences between treatment groups. They will be reported to the IRB on an annual basis, unless they meet the criteria for Serious Adverse Event (see below).

8.1.2 Unanticipated problem

Any incident, experience, or outcome that meets all of the following criteria:

(1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the study.

(2) is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments.

(3) suggests that the participation in the study may place subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Please note that not all adverse events are unanticipated problems and only some unanticipated problems are in fact adverse events. For instance, if a laptop containing study data is stolen, this is an unanticipated problem but it is not an adverse event since it is not an untoward or unfavorable medical occurrence in a human subject

8.1.3 Serious Adverse Event

A serious adverse event is defined as:

1. Unanticipated events possibly related to exposure to study medications such as angioedema, agranulocytosis, hepatic injury, or Stevens Johnson syndrome
2. Other events that are serious AND either related or possibly related to the study which occur at a higher rate than expected in this population
3. Other events that are unexpected AND serious AND either related or possibly related to the study beyond the complications expected in this population

Note that deaths are an expected outcome in this population, and will not be reported as serious adverse events, unless they are determined to be related to study treatment and occur at higher than expected rates in the study population.

8.2 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

8.2.1 Methods and Timing of Assessment

Adverse events (complications) may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits. Adverse events will be assessed for during the index hospitalization and at the 3 month study visit. They will be recorded on study data forms with an indication of whether or not they are thought to be associated with participation in the study.

8.2.2 AE/SAE Grading and Relationship Assignment

Adverse event grading: Adverse events will be graded using standard criteria. Relationship of event to the study procedure will be determined by the study physician.

GRADE 1 (Mild) Transient or mild discomfort (< 48 hours); no medical intervention/therapy required

GRADE 2 (Moderate) Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 (Severe) Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 (Life-threatening) Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Relationship Assignment The relationship of the adverse event to participation in the study will be assessed as either:

Definitely related
Probably related
Possibly related
Unlikely related
Unrelated

8.2.2.1 Adverse Events related to study medications.

The study will capture safety information on LMWH and aspirin, both of which are licensed by the FDA. Complications will be classified as study outcomes (8.1.1), and their relatedness to medication exposure will be assessed by the treating physician**.**

8.2.3 Recording and Documentation

Sites will maintain source documents including but not limited to laboratory and radiology reports, clinical notes and discharge summaries. After review of initial and final reports by the medical monitor, the events may be reclassified at their discretion.

8.2.4. Management of Adverse Events

Adverse Events and Serious Adverse Events will be managed according the medical judgment of the treating physician.

8.3 Adverse Event Reporting Procedures

8.3.1 Local Reporting Requirements.

Study sites must always follow and comply with their own local institution's adverse event reporting requirements. Depending on the local requirements, a site may report events locally and not report those events to the METRC Coordinating Center. Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.3.2 SAE and Unanticipated Problem Reporting Requirements

All Serious Adverse Events that are unexpected AND related or possibly related to the study must be reported to the Medical Monitor and METRC Coordinating Center within 72 hours of being made aware of the event. The MM will review the event within 48 hours of receiving notice of the event, and will make a determination of relatedness as well as the required action (stopping medication, informing other sites, etc). When necessary, the MM may convene the DSMB to discuss an event.

In addition, Unanticipated Problems (UPs) that are not adverse events must also be reported to the METRC Coordinating Center within 14 calendar days after the event has been discovered. SAEs/UPs will be reported to the METRC Coordinating Center by entering the SAE/UP form into REDCAP. REDCap is programmed to automatically send an email to the Coordinating Center for both SAEs and UPs, and to the Medical Monitor in the case of an SAE.

The Medical Monitor for this study is:
Mark Swiontkowski, MD, FACS
Department of Orthopedic Surgery
2450 Riverside Ave., R200
Minneapolis, MN 55454
Telephone: (612) 273-7951
Fax: (612) 273-7959
E-mail: swion001@umn.edu

LMWH and aspirin are available from multiple sources and have generic versions available so consequently there will be variability in manufacturer.

8.3.3 METRC Coordinating Center Reporting Responsibilities

When an event is determined to be unexpected and related to study medication exposure, the Coordinating Center will send a copy of each report received about the event to all clinical sites, with instructions for each to forward the report to their IRB.

Copies of the report will also be sent to the Study PI, and to the DSMB. The MCC will maintain a list of such events for reporting and review at DSMB and Steering Committee meetings.

8.4 Reporting Pregnancy (Replace text with "N/A" if not applicable)

Pregnancy will always be captured on case report forms as a medical event**.** LMWH is considered a category "B" medication – to be used only if clearly needed. Aspirin is considered a category "D" medication – adverse reactions have been found in humans – but only in the third trimester, and no participant who is not pregnant at the time of enrollment will still be on study drugs by the final trimester of the pregnancy. If a woman becomes pregnant while on the study medication, the decision to continue study medication will be made by the local treating physician, and the event will be reported in an Unexpected Event Form. Regardless of whether the medication is discontinued or not, the patient will remain in follow-up until the follow-up period is completed and a report on the outcome will be submitted.

8.5 Type and Duration of the Follow-up of Participants After Adverse Events

Study patients who experience an SAE will be followed until resolution of the event, and a final report will be submitted to the medical monitor, the coordinating center and the pharmaceutical company (if applicable).

8.6 Stopping Rules

The DSMB will review the overall progress of the trial in terms of recruitment, data quality, and event frequency and makes a formal recommendation to the DOD at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications or be stopped.

There are two formal interim analyses and one final analysis planned to assess the harm of aspirin with respect to death (due to PE or VTE prophylaxis). The first will occur after one-third of enrolled patients are followed for 3 months. The second will occur after two-thirds of enrolled patients are followed for 3 months. At each interim analysis, the DSMB will evaluate whether there is an increased risk of death/PE of aspirin relative to LMWH. Specifically, they will assess whether the absolute difference in the risk of death between aspirin and LMWH is greater than 0.36% and whether the absolute difference in the risk of PE between aspirin and LMWH is greater than 3.9%. At each interim analysis, one-sided lower confidence intervals for the difference in risk for death and for PE will be computed. Harm with respect to death or PE will be declared if the lower bound is greater than 0.36% or 3.9%, respectively. For each endpoint, the overall type I error of the interim monitoring procedure will be controlled by using an O'Brien-Fleming spending function to compute the level of the confidence intervals at the interim and final analyses (99.99% at first interim analysis, 99.40% at the second interim analysis and 98.00% at the final analysis). For both the death and PE endpoints, these stopping boundaries will ensure that if the difference between aspirin and LMWH are equal or less than 0.36% and 3.9%, respectively, the probability of declaring harm is less than 2.5%.

8.7 Premature Withdrawal of a Participant

A participant may be withdrawn from the study without consent if the sponsor decides to end the study. Other reasons for removing a participant without consent may include but are not limited to non-adherence with the protocol and/or therapy, inappropriate behavior towards study personnel, and incarceration.

8.8 Replacement of a Participant Who Discontinues Study Treatment

Participants who are withdrawn from the study will not count towards the total sample size accrual and will be replaced. Participants who are lost to follow up and have unknown treatment or outcome status will be counted as lost and will not be replaced.

9. MONITORING

9.1 Site Monitoring Plan

The METRC Coordinating Center will be responsible for site monitoring consistent with ICH/FDA guidelines. Monitoring will include a combination of remote and on-site visits of participating clinical research sites to review the individual subject records, including consent forms, case report forms, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. During the site certification process, the monitors also use remote methods to inspect sites' regulatory files to ensure that regulatory requirements are being followed.

The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, or other regulatory authorities for confirmation of the study data.

9.2 Safety Monitoring Plan

9.2.1 Safety Review Plan by the DSMB

An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality. Two interim analyses will occur, the first after 1/3 patients are at 3 months from enrollment and the second after 2/3 of the patients are at 3 months from enrollment

The DSMB is a multidisciplinary group with a written charge provided by METRC. The DSMB will meet in person to review the protocol. After the trial commences, the DSMB meets twice a year to review data or other issues. The DSMB may request more frequent meetings if necessary to fulfill it charge. It may also request additional safety reports on a more frequent basis. For

example, all serious adverse events (SAE) are reported to the DSMB for their consideration and recommendations as they occur.

At its first meeting the DSMB will review definition of all outcomes, adverse events and serious adverse events and revisions to the protocol made as appropriate. Summary data on adverse events (together with study outcomes) will be monitored by the DSMB at its semiannual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events (complications) by blinded treatment group, by clinic, or in other subgroups requested by the DSMB.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events (complications) and serious adverse events, for transmission to the IRBs at each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.

The DSMB will review semi-annual reports by masked treatment groups of the primary and secondary outcomes as well as all adverse events that are not identified as outcomes per se.

Interim data on safety measures requested by the DSMB are reviewed at each of the scheduled semi-annual full meetings. Analyses will be prepared comparing rates of adverse events by treatment group, by clinical center or by other subgroups as requested by the DSMB. Serious adverse events will be reviewed by the medical monitor as they occur with the option of a teleconference if any DSMB member requests

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size

The study is well powered to address all of the specific aims. The primary driver of size is specific aim 1, which involves non-inferiority for death (due to PE or VTE prophylaxis). We plan for a sample size of 12,200.

For specific aim 1, we assume a non-inferiority margin of 0.36%. This margin is derived from a discrete choice experiment in which patients indicated a willingness to accept a 0.08% increased risk of death (due to clots or clot prevention medicine) in exchange for each of a specific set of benefits of taking aspirin over LMWH. These benefits include their preference for (1) oral vs. injectable medicine, (2) decreased risk of bruising, (3) lower out of pockets costs and (4) 1% reduction in complication rates. Given that we expect a 1.5% reduction in the complication rate, we value the fourth benefit as 1.5 times the value of each of the other three benefits. Thus, we set the non-inferiority margin at 0.36% (0.08% + 0.08% + 0.08% + 1.5*0.08%), as the maximum increased risk of death (due to clots or clot prevention medicine) to which the patients would be indifferent given the hypothesized benefits of aspirin over LMHW use.

We anticipate the rate of clot- and clot prevention medicine-related death to be around 0.25%. However, we also anticipate that a proportion of deaths will be adjudicated as being *potentially* due to clots or clot prevention medicine. If the probability of death (attributable or potentially attributable to either clots or clot prevention) in the LMWH arm is 0.445%, we determined (using simulation) that the proposed sample size will provide (1) an 80% chance of declaring non-inferiority if the probability of death for aspirin is 0.445% (that is, if the probability of death is truly the same in both arms) (2) an 80% chance of declaring harm if the probability of death for aspirin is 1.28%.

If the probability of death (attributable to either clots or clot prevention) in the LMWH arm is 0.25%, we determined (using simulation) that the proposed sample size will provide (1) greater than a 95% chance of declaring non-inferiority if the probability of death for aspirin is 0.25% (that is, if the probability of death is truly the same in both arms) (2) an 80% chance of declaring harm if the probability of death for aspirin is 1.00%.

For specific aim 2, which involves non-inferiority for PE, we considered power associated with a non-inferiority margin of 0.87%. This non-inferiority margin is highly conservative as patients have expressed a willingness to accept this 0.87% increase in clot complications just for the advantage of oral versus injection medication. Based upon the discrete choice experiment, a non-inferiority of 3.9% (0.87% + 0.87% + 0.87% + 1.5*0.87%) is justifiable. Assuming a probability of PE for LMWH of 1.5% and a loss to follow-up rate of 7.5%, we determined (using simulation) that the proposed sample size will provide (1) greater than a 95% chance of declaring non-inferiority if the probability of PE for aspirin is 1.5% (that is, if the probability of PE is truly the same in both arms) (2) an 80% chance of declaring harm if the probability of PE for aspirin is 3.19%.

With regards to specific aim 3, the planned sample size will provide 80% power to detect risk of infection/bleeding from 10% in the LMWH arm to 8.47% in the aspirin, assuming a 7.5% loss to follow-up rate.

The study is overpowered for all secondary aims.

10.2 Randomization

Patients who provide consent to be enrolled in the study will be randomized electronically by the online Data Management System maintained at the Coordinating Center at the Johns Hopkins School of Public Health. Following consent, a randomization code is provided assigning treatment group and whether or not the participant was selected to be prospectively surveyed regarding out of pocket costs and treatment adherance. Randomization tables are encrypted and will not be shared with study investigators. While this study is not blinded, provision of linkages between randomization codes and treatment assignment will follow existing METRC unblinding SOP. Patients will be randomly assigned (within center) using block randomization with variable block sizes to either LMWH or aspirin. Compliance regarding the proper treatment protocols will

be monitored by local Research Coordinators in cooperation with the attending surgeon. Any deviation from the assigned treatment group and the actual treatment received will be recorded.

10.3 Missing Data and Measures to Minimize Bias

Missing data is a serious concern that complicates the interpretation of the study results. For missing baseline data, we will use multiple imputation. We do not expect any missing outcome data for death or clinically significant PE. As with most prospective studies, missing data will be unavoidable, even with excellent follow-up. We will employ the following strategies to address missing data in the design, conduct, analysis and reporting of study results: (1) limit participant burden and inconvenience in data collection, (2) provide compensation for participation and completion in the study; (3) provide pre-study training of investigators and research staff to emphasize the importance of full participation in the study during the consent process (even if the patient is "feeling better"); (3) reimburse study sites based on follow-ups completed rather than on per-patient basis; (4) monitor and report missing data rates during the study and provide on-study reinforcement and support to ensure high follow-up rates; (5) collect information on the reasons for missing data; (6) actively engage participants in the study and educate them about the importance of their participation; and (7) collect surrogate information on participants who miss clinic visits; (8) require sites to go back and fill in missing data using medical record information when applicable; (9) carefully track and collect data on any discontinuations, to include the reasons for discontinuation, who decided that the participant would discontinue; and whether the discontinuation involves some or all types of participation; (10) avoid using single imputation methods and will employ multiple imputation strategies for handling missing information when necessary; (11) analyze data under a variety of modeling assumptions regarding how strongly the missingness mechanism is related to outcomes; (12) conduct sensitivity analyses to evaluate the robustness of the study results to various untestable assumptions about the missing data mechanism; (13) estimate treatment effects (utilizing relevant auxiliary information) under the missing at random assumption; (14) explore the effect of departures from the missing at random assumption using pattern-mixture and selection modeling techniques; and (14) we will account for all participants who enter the study in the reporting or our results whether or not they are included in the analysis.

10.4 Planned Interim Analysis

As described above, an independent Data and Safety Monitoring Board (DSMB) will monitor interim data as the trial progresses to ensure patient safety, review efficacy, evaluate recruitment, and assess overall data quality. O'Brien-Fleming stopping guidelines for efficacy will apply. The interim analysis will occur twice, once when the first third of patients are enrolled, and then again when two thirds of patients are enrolled, and will look specifically at the risk of death/PE among patients receiving aspirin relative to those receiving LMWH. After reviewing the results, the DSMB will then a formal recommendation as to whether the trial should continue unmodified, continue with protocol modifications, or to be stopped.

10.5 Analysis Plan

Patients will be followed for 3 months post-injury. The primary statistical analysis will follow the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized. For the five distinct endpoints under evaluation, no multiple comparison adjustments are planned.

Crossover: We will monitor and calculate crossover rates. Due to insurance issues, we expect greater crossover in the LMWH arm. This will introduce a validity threat by attenuating any effects towards the null. As this is a pragmatic trial and crossover can be expected in the real world, our primary analysis will be based on the intent-to-treat paradigm. However, as a secondary analysis, we will use causal inference techniques (e.g., inverse-probability of treatment weighting, propensity scores) to draw inferences in a counterfactual world without crossover.

Binary Endpoints. Treatment effects for binary endpoints (e.g., death, PE, bleeding/infection) will be estimated using a two-group comparison of proportions; confidence intervals for the absolute risk difference will be reported.

Continuous Endpoints. Treatment effects for continuous endpoints (e.g., satisfaction with care) will be estimated using a two-group comparison of means; confidence intervals for the difference in means will be reported.

Superiority Analyses. Primary Aim 3 will be addressed by computing, at the final analysis, a two-sided 95% confidence interval for the difference in probability of bleeding/infection complications between aspirin and LMWH. Superiority of aspirin will be declared if the upper bound of the confidence interval is less than zero. Alternatively, superiority of LMWH will be declared if the lower bound of the confidence interval is greater than zero. Similarly, Secondary Aims 2 and 3 will be addressed by computing, at the final analysis, a two-sided 95% confidence interval for the difference in mean PSQ-18 and out of pocket costs, between aspirin and LMWH, respectively. Superiority of aspirin will be declared if the lower bound of the confidence interval is greater than zero, with the converse indicating superiority of LMWH.

Non-inferiority Analyses. Primary Aim 1 will be addressed by computing, at the final analysis, a one-sided 98% upper confidence interval for the difference in probability of death between aspirin and LMWH. Non-inferiority of aspirin with respect to death (due to PE or VTE prophylaxis) will be declared if the bound of the confidence interval is less than 0.36%. A 98% upper confidence interval is used to ensure that if the difference between aspirin and LMWH is equal or greater than 0.36%, the probability of declaring non-inferiority is less than 2.5%. Similarly, Primary Aim 2 will be addressed by computing, at the final analysis, a one-sided 98% upper confidence interval for the difference in probability of clinically important PE between aspirin and LMWH. Non-inferiority of aspirin with respect to death will be declared if the bound of the confidence interval is less than 3.9%. A 98% upper confidence interval is used to ensure that if the difference between aspirin and LMWH is equal or greater than 3.9% the probability of declaring non-inferiority is less than 2.5%. For these endpoints, there are two ways of making an error when the difference between aspirin and LMWH is equal to the indifference threshold:

declaring harm or declaring non-inferiority. The statistical procedure we have described controls the overall error rate to less than the 5% level. Secondary Aim 3 will be addressed by computing, at the final analysis, a one-sided 95% upper confidence interval for the difference in probability of minor clotting between aspirin and LMWH. The non-inferiority of aspirin will be declared if the upper bound of the confidence interval is less than 3.9% (conservative).

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

Quality Control (Q/C) and Quality Assurance (Q/A) procedures that apply to all studies are outlined in the METRC Manual of Operations (MOP). A certification process will be used as a basis for training and certification of the study personnel involved in data collection. In addition to consortium wide training and certification procedures, additional requirements may be added based on the nature of the study. Ongoing data edits and audits will be performed to ensure collection of quality data. The continuous and timely flow of data from the centers to the MCC is an essential prerequisite for maintaining data quality.
Monthly enrollment reports will be distributed to each center that will summarize recruitment, data completion and timeliness of data entry. These reports will also include a set of queries generated by REDCap and sites will be asked to address these queries within 10 business days.

11.2 Training and Certification of Centers

All participating centers together with their respective study personnel will undergo certification that included training, local site IRB, and a knowledge assessment on the study design and procedures. This training will include a training for research coordinators in the submission of regulatory documents, data collection procedures, and study follow-up, as well as meetings between the PI, study project director, and the study team at each site to ensure that the procedures are well understood prior to engaging with research subjects.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 IRB/Ethics Committee

IRB approval will be obtained from the MCC at Johns Hopkins Bloomberg School of Public Health, the University of Maryland School of Medicine, and each participating clinical site according to METRC policies and procedures. Sites that recruit patients will submit METRC study recruitment materials to their organization's IRB prior to use at that facility.
Sites must provide the Coordinating Center with a copy of the initial IRB approval notice and subsequent renewals as well as copies of the IRB approved consent statements.
No site can begin work related to this study until the site has been certified by the MCC in accordance with METRC policies and procedures.

12.2 Exclusion of Women, Minorities, and Children (Special Populations)

The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (African-Americans, Asian-Americans and Hispanics) as well as non-Hispanic white subjects.

***The study will not include children or prisoners*.**

12.3 Participant Confidentiality

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission to the Data Coordinating Center.

Patients will be identified in the central data collection system, REDCap only by an identification code but not by their name, SSN, or hospital medical record number. Study Site Investigators will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses available only to local clinic staff certified by the MCC to participate in the study.

The subset of the participants who agree to participate in the adherence study will sign a HIPAA authorization form allowing their contact information to be shared with the coordinating center so that follow up calls can be made.

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the sponsor (MCC), IRB, DOD, or DSMB. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB and DOD requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

12.4 Study Discontinuation

Participants will be informed that they may discontinue the study at any time, for any reason. They will be assured that the medical care which they receive at the participating facility will not be affected should they elect to discontinue participation in the study.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Each study site is responsible for collecting and uploading study data in a timely fashion. The research coordinators at each site will obtain the information necessary to complete the electronic case report forms (eCRFs) from several sources including but not limited to, the patient's medical record, clinical evaluations and patient interviews. The Site Research Coordinator will enter non-personally identifiable information into a central /and secured web-based data management system being implemented for all Consortium studies, known as REDCap. This data management system has incorporated state-of-the-art features for electronic data collection and is configured in accordance with best practices for information technology and research data management.

The PI will certify completeness and accuracy of the study data at two time points: once following completion of all baseline data and treatment information, and then again following completion of the 3 month visit. This will take place through review of a summary of data in REDCap and a certification that data collected for the study are true and accurate.

All research data, in hard copy or electronic form, will be stored and managed in a secure manner following applicable federal regulations and ICH guidelines and according to institutional policies and practices. Hard copy documents generated by the sites which contain subject data, patient identifiers and contact information will be stored in secure, locked containers (file cabinets, drawers, etc.) in accordance with standard document management practices.

At all times only MCC-certified key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents, including electronic data and medical records. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct. This information will be available for audit by study monitors and representatives of the local IRB and the MCC.

13.2 Data Capture Methods

Data will be collected in real time by the investigator or study coordinator directly on electronic Case Report Forms (CRFs).

13.3 Types of Data

Data will include: medical and surgical histories, laboratory reports, radiology reports, clinical evaluations, medication administration records, adverse events and patient interviews.

13.4 Source Documents and Access to Source Data/Documents

Source documents laboratory results, patient surveys, medical records, etc. will be maintained at the site and will be made available to study monitors, and representatives of regulatory agencies including the MCC and IRB.

13.5 Study Records Retention

Study records will be maintained in accordance with current ICH guidelines. Data will be maintained for five years following the end of research-related activities, including data cleaning and analysis. At the end of this period, each site will provide the Coordinating Center a signed verification that these data have been destroyed.

13.6 Protocol Deviations

Records of protocol deviations will be noted on the Protocol Deviation CRF (AF05) with the reason for the deviation recorded, as well as any action taken to mitigate the deviation. This information will be entered into REDCap. These records will be provided to the site's IRB in accordance with local reporting requirements and be made available to study monitors.

14. PUBLICATIONS POLICY

Publications will be written in accordance with the METRC publication policy (available on the METRC website: www.metrc.org).

15. SCIENTIFIC REFERENCES

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17. APPENDICES

APPENDIX A: STUDY CONTACT ROSTER

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APPENDIX B: DATA COLLECTION SCHEDULE

Assessment	Baseline	Baseline – 3 months	3 month
CRF00: Inclusion/Exclusion	X		
CRF01: Patient Contact Information	X		
CRF02: Patient Characteristics	X		
Demographics • DOB • Age • Sex • Race • Height • Weight • Tobacco use • Health Insurance • Education			
CRF03: Medical History	X		

• Medications taken Prior to Injury
  ○ OCP or Estrogen use
  ○ Antiplatelet agent
  ○ ASA daily use
  ○ Blood thinners
  ○ NSAIDs (daily use or prescription)
• Co-morbidities
  ○ Charlson Comorbidity Index
  ○ History of VTE, peptic ulcer, DM
  ○ Cancer
  ○ Immunosuppression			

CRF04: Injury Characteristics	X		
• Injury date/time • Circumstances • Type of Injuries (orthopaedic/non-orthopaedic) • Side of Injuries • AO/OTA Fracture classification • Gustilo Classification • Tscherne Classification of Soft Tissue Injuries • Injury Severity Score, TRISS, ICU days, ventilator days			
CRF05: Index Hospitalization	X		
• Admission date/time			

Assessment	Baseline	Baseline – 3 months	3 month

• Discharge date/time
• Discharge outcome (discharged/death)
• Admission labs (if tested)
  ○ INR
  ○ PTT
  ○ Platelets
  ○ Max serum lactate (first 24 hours)
  ○ Creatinine
  ○ TEG parameters (if ordered)
• Surgical data
  ○ Surgery info (ortho/non-ortho surgeries)
  ▪ Dates
  ▪ Total number of surgeries
  ▪ Weight bearing status on discharge
  ○ Total number of surgeries (ortho/non-ortho)
• Imaging studies (and results) conducted for bleeding or VTE
  ○ Angiogram
  ○ Ventilation perfusion (VQ) scan
  ○ Duplex scan/ultrasound
  ○ CT angiogram (CTA)
  ○ MRI
  ○ Other
• Complications
  ○ fatal bleed
  ○ ≥2g/dL drop in hemoglobin
  ○ reoperation for hematoma evacuation
  ○ other clinical significant bleeding
  ○ infectious complication
  ○ VTE
  ○ PE
• Concomitant meds
  ○ LMWH
  ○ Aspirin
  ○ Plavix
  ○ platelet inhibitors
  ○ NSAIDs
  ○ Anticoagulation medications outside treatment assignment			

CRF06: VTE Prophylaxis (Inpatient)	X		

Assessment	Baseline	Baseline – 3 months	3 month
• Pre & Post Randomization Prophylaxis Use • Treatment Arm: Aspirin Dosage (Dose, Dose Unit, Route, Date/Time of Start/Stop of Administration) • Treatment Arm: LMWH Dosage (Dose, Dose Unit, Route, Date/Time of Start/Stop of Administration) • Reasons prophylaxis held or discontinued (if applicable) • Doses ordered vs doses received or missed & reason missed • Treatment crossover information: number of doses & therapeutic anticoagulation therapy status (date, dose, reason)			
CRF07: Clinical Follow-up			X

• Documented prescribed prophylaxis and duration
• Out of pocket costs
• Satisfaction
• Prescribed medications
• Any other treatment for PE/VTE event
• Re-hospitalizations related to PE/VTE event– review medical records
• Imaging studies
• Post discharge surgeries
  o Planned elective surgeries
• Complications (type, severity, treatment)
  o Fatal bleed
  o GI bleed
  o ≥2g/dL drop in hemoglobin
  o reoperation for hematoma evacuation
  o other clinical significant bleeding
  o infectious complication
  o VTE
  o DVT (blood clot in arms/legs)
  o Pulmonary Embolism
  o Imaging studies for bleeding or VTE
  o Surgical wound infection
  o Surgical wound hematoma
  o Abnormal postoperative bleeding
  o Any complications secondary to treatment since hospitalization			

Assessment	Baseline	Baseline – 3 months	3 month
CRF08: Patient Follow-up			X
• Hospitalizations r/t PE/VTE outside the study center • PSQ-18 Patient Satisfaction Questionnaire			
CRF09: Diagnosis of Infection	X	X	X
• CDC Criteria • Culture Data • Lab Data • Imaging Studies • Wound Characteristics • Time to Wound Closure • Type of Soft Tissue Coverage • Limb Complications (type, severity, treatment)			
CRF10: SAE	X	X	X
Unanticipated events possible related to exposure to study medications (angioedema, agranulocytosis, hepatic injury, Stevens Johnson syndrome), other events that are serious and either related or possibly related to the study, other events that are unexpected and serous and either related or possibly related to the study beyond the expected complications.			

ATTACHMENT C: CONSENT FORM
JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

INFORMED CONSENT DOCUMENT

Patient Consent Form

Study Title: PREVENTion of Clot in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

Principal Investigator: Robert O'Toole, MD (Clinical PI) and Renan Castillo, PhD (Research PI)
IRB No.:
PI Version Date: Version 1; 03/06/17

You are being asked to volunteer to be a part of a research study. Please read this form carefully before you sign it. This consent form explains the research study and your part in the study. If you decide not to participate in this study there will be no impact on your medical care. You can choose not to take part and if you join, you may quit at any time. Ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand. Ask as many questions as needed. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

The purpose of this research study is to help determine the best treatment for preventing blood clots that are formed following trauma like yours that could potentially lead to death. At the moment researchers do not know if using medications called low molecular weight heparin or aspirin is better in preventing life threatening blot clots in trauma patients. In this study, we are trying to answer this question. Usually either low molecular weight heparin is given by subcutaneous (under the skin) injections (liquid) medicine or aspirin (pill) medicine is given by mouth while in the hospital and after you go home to prevent blood clots. There has not been a study to compare these two types of medicines for preventing blood clots in trauma patients and order to find out which medicine is best this study will compare these two forms of treatment.

The PREVENT CLOT Study is funded by the Patient-Centered Outcomes Research Institute (PCORI) and is being carried out in more than 20 major trauma centers across the United States and Canada, including military centers that are taking care of service members who were injured in the line of duty.

2. WHY AM I BEING ASKED TO PARTICIPATE?

You are being asked to join this study because you are at least 18 years old and have experienced a traumatic orthopaedic injury(ies) which puts you at increased risk of blood clots and also you are currently being treated with blood clot prevention medicine. People like you who are being treated at major trauma centers from around the county are being asked to participate. You are one of over 12,000 patients expected to join the PREVENT CLOT study.

3. HOW LONG WILL THE STUDY LAST?

If you agree to participate in this study, you will be followed for up to three months after admission to the hospital for your traumatic injury.

4. HOW DOES THE STUDY WORK?

If you agree to participate in the PREVENT CLOT Study you will be assigned by chance (like flipping a coin) to one of the two treatments being studied:

- Treatment A: Low molecular weight heparin (Lovenox/Enoxaparin) medicine given two times a day subcutaneously (under the skin) by injections.
- Treatment B: Aspirin medicine given two times a day in pill form by mouth.

You have an equal chance of getting any of the treatments. We are using this method for deciding which treatment you will get because it is not clear at the present time which treatment is better at preventing blood clots for you and for people like you with similar injuries.

You will begin receiving medicine immediately after you are enrolled. When you are discharged from the hospital you will continue taking the medicine you were assigned for the same period of time as if you were not in the study. Your doctors will prescribe the correct length of time for you to take this medicine based on the types of injuries you have and any other medical conditions you may have. Some people do not take any more medicine when they leave the hospital, and others can take the medicine for several months.

A group of randomly selected participants will be contacted and asked to report on how many times they take their medication daily at home. If you are one of the selected individuals you will receive a phone call or email from the research team and will be asked a few questions on how many medicine doses you have taken so far.

When you come back for normal clinical follow up visit to see your surgeon at 3 months after your hospital admission you will be asked to complete a 15-30 minute interview where you will be asked questions about how your recovery is going and your overall satisfaction with your care. If you are not able to come back, we may contact you by telephone or email to do these interviews.

5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

There are some risks related to taking either medication in this study. If you experience any of the risks listed below please immediately proceed to the nearest emergency room and let then let the study team know as soon as possible: signs of bleeding (vomiting blood or vomit that looks like coffee grounds; coughing up blood; blood in the urine, black, red or tarry stools, bleeding from the gums, abnormal vaginal bleeding; bruising without a reason or that get bigger; or any severe or persistent bleeding), severe dizziness, fainting, fall or head injury, confusion, severe headache, burning or numbness feeling or loss of strength. Signs of significant allergic reaction – wheezing, chest tightness, fever, itching, tight cough; change in skin color; seizures or swelling of face, lips, tongue or throat. The risks of taking either medication are as follows:

- Treatment A (Low molecular weight heparin (enoxaparin)): nausea; diarrhea, injection site irritation, bruising, pain or possible infection; allergic reaction ranging from hives and itching to difficulty breathing or throat swelling; Heparin Induced Thrombocytopenia which results in a reduced number of platelets and impaired ability to form clots; bleeding complications which could require transfusion or operation and kidney damage.
- Treatment B (Aspirin): Risk of inflammation or ulceration of the stomach, allergic reaction (ranging from hives and itching to difficulty breathing or throat swelling), ringing of the ears, and worsening asthma. Increased risk of bleeding and of kidney damage. Potential risk of risk of Reyes syndrome in younger partitipants during influenza season. Symptom of Reyes syndrome include: fever, lack of energy or interest in things, sleepiness, changes in personality, vomiting or diarrhea.

6. WHAT ARE THE POTENTIAL BENEFITS?

You will not benefit directly from your participation in this study. Your participation in the study could help us determine the best treatment to prevent life threating blot clots resulting from injuries like yours. This information could be very helpful to other people who have this same injury in the future.

7. DO I GET ANY PAYMENT FOR BEING IN THE STUDY?

You will receive an honorarium in recognition of your time and effort. $20 will be given to you for completing the **3** month visit in appreciation for your time and effort. If you complete follow-up activities by phone or email will also be given $20 for competing the interview.

8. ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?

There are no additional costs for taking part in this research study above the reasonable and customary costs of caring for patients with injuries like yours who are not in the study.

9. WILL MY INFORMATION BE KEPT PRIVATE?

The information we collect from you will be kept private to the best of our ability. Your name, birth date, medical record number and any other information that could identify you as an individual will be removed from all study forms. Instead, we will label your forms with a unique study number. The link between your name and your study number will be kept confidential to the greatest extent provided by law. The information collected for the study will be stored in a password protected, HIPAA compliant computer database that only authorized members of our research team can use. When we report the results of the study, we will combine the information about you with similar information about hundreds of other people so your individual information will not be identifiable.

All study records will be considered confidential, and your name will not be used in reports or publications.

10. WILL YOU SHARE MY INFORMATION WITH OTHERS?

We will use your information only for the purposes of this study. The data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted will be allowed to inspect sections of your medical and research records related to the study. This includes people designated by The Johns Hopkins Bloomberg School of Public Health who are overseeing this study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

The Patient-Centered Outcomes Research Institute (PCORI) is providing funding to sponsor this study. PCORI representatives and your local IRB may have access to research records in their role to protect human subjects engaged in research.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?

Your alternative is to not take part. If you choose not to take part, your healthcare will not be affected.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?

Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.

Your participation in this research study could be ended without your consent. Possible reasons could include our decision to end the study early or other reasons.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or become ill because of your participation in this study, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

You do not give up any of your legal rights by signing this form. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff or others.

14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

- <<insert name>>, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact << insert him/her>> at <<telephone number>>. You may also call the Director of the Study at your hospital, <<insert name>>, at <<telephone number>>.
- If you have further questions about your rights as a study participant you can call or contact the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

  Address: Johns Hopkins Bloomberg School of Public Health
  615 N. Wolfe Street, Suite E1100
  Baltimore, MD 21205
  Telephone: 410-955-3193
  Toll Free: 1-888-262-3242
  Fax: 410-502-0584
  E-mail: irboffice@jhsph.edu

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature (or thumbprint/mark) on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____ _____ _____

Print name of Adult Participant Signature of Adult Participant Date

_____ _____ _____

Print name of Legally Authorized Representative (LAR) Signature of LAR Date

_____

Relationship of LAR to Participant

Ask the participant to mark a "left thumb impression" in this box if the participant (or participant's parent) is unable to provide a signature above.

_____ _____ _____

Print name of Person Obtaining Consent Signature of Person Obtaining Consent Date

Give one copy to the participant and keep one copy in study records

Major Extremity Trauma Research Consortium (METRC):

PREVENTion of Clot in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

Sponsored by: PCORI

Contract Number:
PCS-1511-32745

IND#

IDE# *N/A*

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This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from METRC (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

Table of Contents

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List of General Abbreviations/Terminology

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DVT	Deep Venous Thrombosis
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LMWH	Low Molecular Weight Heparin
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
OHRP	Office for Human Research Protections
PE	Pulmonary Embolism
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAB	Stakeholder Advisory Board
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
VTE	Venous thromboembolism

PROTOCOL SUMMARY

Title: Prevention of Clots in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

Sponsor: Patient Centered Outcomes Research Institute (PCORI)

Type of study: Randomized Pragmatic Trial

Objective: *To compare aspirin versus low-molecular weight heparin (LMWH) (Enoxaparin) as a thromboprophylaxis in patients who sustain a fracture.*

We aim to make the following comparisons between aspirin and the LMWH:

Specific Aim 1: Compare the proportion of patients who die after orthopaedic trauma treated with LMWH compared to those treated with aspirin. (Hypothesis 1: Aspirin will be non-inferior to LMWH.)

Specific Aim 2: Compare the proportion of patients who sustain non-fatal PE or deep vein thrombosis (DVT) after orthopaedic trauma treated with LMWH compared to those treated with aspirin. (Hypothesis 2: Aspirin will be non-inferior to LMWH.)

Specific Aim 3: Compare the proportion of patients who sustain a bleeding event, a wound complication, or deep surgical site infection (SSI) after orthopaedic trauma patients treated with LMWH compared to those treated with aspirin. (Hypothesis 3: The rate of complications will be superior (i.e., lower) in the aspirin group compared to LMWH.)

We will pursue the following secondary aims:

Secondary Aim #1: Assess satisfaction with care in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 4: Satisfaction will be superior in the aspirin group.)

Secondary Aim #2: Estimate out of pocket patient costs in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 5: Out of pocket costs will be lower in the aspirin group.)

Study duration: 5 years: 1 year of planning, 3.5 years of recruitment and follow-up, 0.5 years of analysis and dissemination of study results

Sample size: 12,200 (6,100 per arm (2) arms)

Number of study sites: up to 30

Study population: Orthopaedic trauma patients, ages 18 and over

Inclusion criteria:

1. Does the patient have a planned operative or non-operative pelvis or acetabular fracture, or any operative extremity fracture proximal to the metatarsals/carpals?
2. Is the patient at increased risk of blood clot(s) from their orthopaedic injury(ies) and will receive a prophylactic blood thinner regimen per standard of care?
3. Is the patient 18 years or older?

Exclusion criteria:

1. Did the patient present to the hospital more than 48 hours post injury?
2. Has the patient received more than 2 doses of LMWH or Aspirin for initial prophylaxis?
3. Is the patient on long term blood thinners (other than low-dose aspirin or platelet inhibitors such as Plavix or Aggrenox)?
4. Did the patient have a VTE within the last 6 months?
5. Is the patient on therapeutic (as opposed to prophylactic) blood thinners for an acute issue at the time of admission?
6. Does the patient have a newly diagnosed indication for therapeutic blood thinners (for example vascular injury) that will require therapeutic anticoagulation for more than one week?
7. Does the patient have an allergy to aspirin, or NSAIDs, or a history of heparin induced thrombocytopenia, or other medical contraindication to blood thinners (e.g. peptic ulceration, gastrointestinal bleeding, etc.)?
8. Is the patient on higher dose aspirin (>81 mg once a day or higher) for medical reasons or will be treated with higher dose aspirin?
9. Does the patient have underlying chronic clotting disorders (i.e. Factor V Leiden, hemophilia, Protein C and S deficiency) that require full dose anticoagulation or are a contraindication to VTE chemoprophylaxis?
10. Does the patient have end stage renal disease, or impaired creatinine clearance <30 ml/min at time of randomization?
11. Is the patient pregnant or lactating?
12. Does the patient speak neither English nor Spanish?
13. Is the patient a prisoner?
14. Is the patient likely to have severe problems maintaining follow-up?
15. Is the patient, based upon the clinical judgment of the treating clinician, NOT equally suited for treatment with either Aspirin or Lovenox?

16. Should the patient be excluded for other reasons at the discretion of the treating physician?

17. Does the patient have a known COVID-19 diagnosis prior to fracture treatment or within 3 months of the index fracture?

Outcome measures: All-cause mortality, cause-specific mortality, non-fatal pulmonary embolism, deep vein thrombosis, bleeding event, wound complication, deep surgical site infection, satisfaction, out of pocket patient costs

Statistical analysis: Non-inferiority intention to treat analysis for study primary aim.

Randomization: Block randomization at the center level.

Safety monitoring: The Medical Monitor is responsible for monitoring serious adverse events (SAEs) as the study progresses to ensure patient safety. The DSMB will review all safety data at its scheduled meetings. The Medical Monitor may convene a meeting of the DSMB to evaluate any SAEs that he/she determines require immediate attention.

Data Safety and Monitoring Board (DSMB): The DSMB is an independent body responsible for evaluating recruitment, safety and outcome data. The DSMB has the authority to stop the study based on its findings.

1. KEY ROLES

Protocol Committee- Responsible for developing a detailed study protocol, provides oversight on study progress and acts to correct deficiencies in the conduct of the study. This committee also drafts the main publications related to the study.

Steering Committee- The Science Committee of the METRC Consortium will review the composition of the protocol committee and provide scientific review of the study protocol, with the purpose of presenting the protocol to the Consortium Steering Committee for approval. Additionally, the study will have a Steering Committee comprised of the study investigators, an orthopaedic and general surgery investigator from each participating center, 2-3 experts on clot prevention, and the patient and consumer stakeholders who comprise our Stakeholder Advisory Committee.

METRC Coordinating Center- Responsible for maintaining all study documentation, developing and maintaining the master IRB application and consent, circulating any changes to study documents including protocols, case report forms, and IRB materials to each participating center, providing daily oversight and management of study implementation, providing payment to sites for patients enrolled, performing site monitoring, data quality control and analysis of study results.

Clinical Sites- Responsible for the conduct of clinical studies including patient enrollment, performing study procedures, data collection and conducting study follow-up visits.

Clinical Outcome Adjudication Committee (COAC)- This committee will be responsible for developing the timely medical review and adjudication of trial-specific endpoints utilizing trial-specific definitions; engages other reviewers as needed and in accordance with the COAC Policy; and reports adjudication results to the trial-specific Protocol Committee.

Publication Committee- Responsible for reviewing manuscripts prior to journal submission and reviewing presentations prior to presentation; for mediating and settling disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations; for preparing and maintaining a list of concepts for publications and preparing and maintaining a list of approved METRC publications, which shows the status of each manuscript from initiation through publication.

DSMB- Independent Data and Safety Monitoring Board (DSMB) convened for this project, responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality.

Medical Monitor- Responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety

goals and objectives. This is achieved through the review of safety reports; resolving safety issues; and interacting with Principal Investigators.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Importance of Blood Clots and Blood Clot Prevention Medicines. Preventing venous thromboembolism (VTE) in the legs or lungs is a major unsolved problem in modern medicine. Each year, in the United States alone, blood clots are estimated to affect 300,000 – 600,000 patients.[1] These events may have important consequences for patients. VTE can include both deep venous thrombosis (DVT) and pulmonary embolism (PE). Even minor blood clots require a minimum of 6 months of medication, often with frequent blood tests, and increased risk of medication-related bleeding. At the most severe end, PEs are thought to account for 60,000–100,000 deaths per year in the United States.[2]

Patients who sustain trauma are well known to be at an increased risk for blood clots throughout their body, including fatal PE's.[3] There are 6 million fractures treated each year in the United States alone and 2.3 million patients are admitted each year after trauma.[4-6] Hip and femur fractures specifically are among the most common fractures and are associated with a particularly high risk of blood clots.[7,8] Current guidelines indicate that most orthopaedic trauma patients should be given medication to reduce the risk of blood clots.[9,10] Despite the common nature of these injuries and the potential devastating impact that blood clots can have on patients' lives, we currently do not know the best prophylactic regimen for these patients.

The ideal clot prevention medication for orthopaedic trauma patients would prevent death from PE and other consequences of blood clots while also limiting complications from the medication, such as bleeding from surgical wounds and other sources.[11] A blood clot resulting in death is obviously a devastating outcome for a patient and their family; however, other complications from clot prevention medications are not insignificant and may require surgery and have a major impact on the lives of patients, including, permanent disability in some cases.[12,13] Even under ideal conditions the medications used to reduce clots cannot completely eliminate the chance of blood clots and in some instances may lead to death themselves.[12-14]

Low molecular weight heparins (LMWH) are medications that have been utilized to lower the rates of proximal deep venous thrombosis in trauma patients since the 1990's and are currently the preferred agents across many guidelines, including those from the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma.[9,10] The case for the use of LMWH in this trial is relatively straight forward as it is the current treatment recommended by these guidelines and is commonly used in most north American trauma centers. While these guidelines are well intentioned, they are based on limited evidence regarding fracture patients, and do not incorporate patient preferences. There is good evidence that LMWH's are effective at limiting DVT, particularly asymptomatic DVT found on screening studies as a part of a research protocol.[3,15,16] However feedback from patients indicates that they are more concerned with PE's

that might cause death or clot prevention medication-related complications that require surgical treatment, rather than blood clots in the leg that are often asymptomatic or of minimal clinical consequence. This was confirmed by our own pilot research (conducted under a separate IRB). We interviewed 232 orthopaedic trauma patients and found that patients value the prevention of death and avoidance of surgical complications much more than other issues related to clot prevention medications.[17]

Despite the widespread use of LMWH to reduce PE after orthopaedic trauma, a recent Cochrane review actually showed limited evidence that LMWH affects the rate of PE or mortality in trauma patients,[3] and there is concern that there is potential for higher rates of bleeding into critical organs and surgical wounds associated with LMWH compared to other clot prevention medications in non-trauma related orthopaedic surgery.[18-20] This has led many to wonder if there is another alternative to clot prevention than LMWH for trauma patients.

Aspirin is another commonly used clot prevention medication, which may have a similar efficacy at preventing both PE and death in lower extremity injuries.[21] For both hip fracture and lower extremity arthroplasty surgery, substantial reductions in surgical wound hematomas have been noted with aspirin.[22] In addition, after lower extremity arthroplasty, LMWH has been associated with higher all-cause mortality as compared to the use of aspirin.[12] Although there are certainly strong advocates for the use of aspirin in orthopaedic trauma patients and some solid studies in arthroplasty supporting its use,[21,23-25] the efficacy of ASA has not been characterized relative to LMWH in this population yet.

No Data for Guidelines: A recent study on this topic by the Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlighted a knowledge gap surrounding clot prevention in orthopaedic trauma patients and concluded that there is "wide variability in practice patterns, poor scientific support for various therapeutic regimens" and guidelines are needed to "improve patient care."[26] As demonstrated by this study, there is a clear need for guidelines on clot prevention in trauma patients,[26] but there are no large high quality trials upon which to base these guidelines, as described by the Cochrane review on this topic.[3] Most of the existing guidelines make recommendations that are based on either arthroplasty patients (who are a poor surrogate for trauma patients), or an older subset of hip fracture patients, limiting the applicability to the vast majority of patients who fundamentally differ from either of these groups. Unfortunately, this knowledge gap leaves clinicians and patients to make decisions about which VTE prophylaxis to use in this large patient population without adequate data to guide them.

2.2 Rationale

The best medication to reduce the risk of fatal PE for orthopaedic trauma patients who are admitted to a hospital after trauma each year in the United States is still unknown, creating decisional uncertainty for both patients and clinicians.[26] Recent meta-analysis on medications to prevent blood clots after major lower extremity surgery included no studies involving high energy trauma and only two small studies on hip fractures, concluding that "the rarity of

pulmonary embolism made meaningful comparisons between aspirin and anticoagulation impossible …"[22] The rarity of PE requires a large trial to answer this question and none exist to date. Similarly, a recent Cochrane review on this topic in trauma patients did not address the use of aspirin for clot prevention presumably due to a complete lack of data on the topic.[3]

There is little data on how commonly used medications like LMWH perform in trauma patients relative to enteral aspirin, likely because of the large patient sample size needed to address this issue. Moreover, the currently limited research in this topic has focused more on clinically insignificant DVTs, and have not been powered to address the outcomes most important to patients and clinicians, including bleeding complications and fatal PE.[3,22]

In addition to the lack of guidelines to support clinical decision making, there is a lack of evidence on how the choice of chemoprophylaxis following orthopaedic trauma affects patient satisfaction. Factors that are important to patients such as the need for the medicine to be injected or the out of pocket costs have been almost totally ignored to date.[3,22,26,27]

To address these critical gaps in the evidence we have designed a large, pragmatic, multicenter randomized clinical trial. This trial will provide definitive evidence for decision makers on whether aspirin is as effective as LMWH at preventing death and symptomatic PE, while potentially resulting in significantly fewer medication associated complications. The study fills several large and critical knowledge gaps of great interest to patients and clinicians and has great potential to improve the quality of evidence available for patients and other stakeholders to make informed decisions.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks The risks associated with participation in this study are primarily the risks that are associated with each of the study drugs.

Patients randomized to the LMWH arm would have no drug-related risk over and above the risk they would experience as standard of care. These risks include bruising or infection at the site of injection and allergic reaction, ranging from hives and itching to difficulty breathing or throat swelling. Some participants may experience Heparin Induced Thrombocytopenia, which results in a reduced number of platelets and hypercoagulability. Risks associated with the LMWH arm also include bleeding complications, which could require transfusion or operation, and kidney damage.

Patients randomized to the aspirin arm would have no drug-related risk over and above the risk they would experience as using aspirin for blood clot prevention. These risks include the potential to experience the risks associated with aspirin, including possible risk of inflammation or ulceration of the stomach, allergic reaction (ranging from hives and itching to difficulty breathing or throat swelling), ringing of the ears, and worsening asthma. Additionally, some patients have increased risk of bleeding and of kidney damage.

There is potential that patients in the aspirin arm will be at lower or higher risk relative to the patients in the LMWH arm just as there is a risk for patients in the LMWH arm to have better or worse outcomes than those in the aspirin arm. The trial is designed to assess this potential difference in risk.

A DSMB for the study will closely monitor event reporting, and should differential risks or benefits be identified, will consider stopping the study.

In this study, as with many others, there is a potential risk of breach of confidentiality, although the study team will make all reasonable efforts to mitigate this risk.

2.3.2 Potential Benefits It is not clear that one drug treatment will provide any benefit over another. Patient participants will receive $20 as compensation for time and effort returning for the 3-month study visit.

3. STUDY OBJECTIVES & OUTCOMES

3.1 Primary Objective:

We aim to make the following comparisons between aspirin and the LMWH:

Specific Aim 1: Compare the proportion of patients who die after orthopaedic trauma treated with LMWH compared to those treated with aspirin. (Hypothesis 1: Aspirin will be non-inferior to LMWH.)

Specific Aim 2: Compare the proportion of patients who sustain non-fatal PE or deep vein thrombosis (DVT) after orthopaedic trauma treated with LMWH compared to those treated with aspirin. (Hypothesis 2: Aspirin will be non-inferior to LMWH.)

Specific Aim 3: Compare the proportion of patients who sustain a bleeding event, a wound complication, or deep surgical site infection (SSI) after orthopaedic trauma patients treated with LMWH compared to those treated with aspirin. (Hypothesis 3: The rate of complications will be superior (i.e., lower) in the aspirin group compared to LMWH.)

3.2 Secondary Objectives:

We will pursue the following secondary aims:

Secondary Aim #1: Assess satisfaction with care in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 4: Satisfaction will be superior in the aspirin group.)

Secondary Aim #2: Estimate out of pocket patient costs in orthopaedic trauma patients treated with injectable LMWH compared to those treated with aspirin. (Hypothesis 5: Out of pocket costs will be lower in the aspirin group.)

3.3 Study Outcomes

To meet study objectives, the following clinical outcomes will be assessed:

3.3.1 Primary Outcome

All-Cause Mortality

The primary outcome for this study is all-cause mortality by 90 days post-randomization. The primary study outcome was changed from PE-related death to all-cause mortality during the course of the trial. At the recommendation of an external peer reviewer for the protocol manuscript, the trial's steering committee determined that it was unfeasible to adjudicate death due to pulmonary embolism (PE) with reasonable certainty. Misclassification of the primary outcome of PE-related death would bias the results to non-inferiority. As such, the trial's steering committee decided to change the primary outcome from PE-related death to all-cause mortality. All-cause mortality was viewed as more important than PE-related death by our patient stakeholder and protocol committees and had greater scientific reliability. The DSMB was not involved in these decisions due to their knowledge of treatment effect from interim analyses. The decision of the trial's steering committee to change the primary outcome and non-inferiority margin was supported by the protocol committee, patient stakeholder committee, and sponsor.

3.3.2 Secondary Efficacy Outcomes

Cause-Specific Death

Cause-specific death will remain as a secondary outcome. Cause of death will be recorded in addition to an assignment of certainty of the attribution. The study's 3-person Clinical Outcome Adjudication Committee (COAC) is composed of experts not otherwise involved in any other aspect of the study. The committee is blinded to treatment arm and receives these data with the goal of classifying the death into 1 of 5 categories: a) *Certainly PE* (e.g., an autopsy or operative note indicates cause of death), b) *More likely to be caused by PE than something else* (e.g., clinical information available indicating likely cause of death, but no autopsy or corroborating data available), c) *Equally likely to be caused by PE or something else* (e.g., patient did not die in a clinical setting, and only data available to support assignment of causality is based on the report on non-clinical family or friends), d) *More likely to be a cause other than PE* (e.g., the clinical course was highly suggestive that the cause of death was not PE), and e) *Certainly not due to PE* (e.g., the cause of death was not related to a PE). There must be agreement among at least 2 of the 3 committee members, with no more than 1 level of disagreement among members, for the cause of death category determination to be finalized. We will report cause-specific death as: i) category a or b; ii) category a, b, or c; iii) category d or e.

Non-Fatal Pulmonary Embolism

Non-fatal PE is a key secondary outcome. The local site investigators categorize PE events, which are adjudicated centrally as one of four levels: *Massive* and *submassive* PE events are

defined based on the American Heart Association recommendations[24]; *Other clinically significant* PE events are determined when a diagnostic test was performed due to symptoms or signs concerning for PE, but the symptoms or signs do not meet the *massive* or *submassive* criteria; *Other clinically insignificant* PE events include PEs found incidentally, or as part of a test performed for screening, or for another reason that does not meet the definition of "clinically significant." Additionally, PE events are sub-classified as being segmental or non-segmental. Similar to the adjudication of the cause of death, the categorization of PE requires two-thirds consensus from the COAC. We report non-fatal PE as: i) any level; ii) sub-classified as massive, sub-massive, clinically significant, clinically non-significant; and iii) sub-classified as segmental, non-segmental.

Deep Vein Thrombosis (DVT)

DVT can be either symptomatic or asymptomatic and require a confirmed imaging diagnosis. We will report all confirmed symptomatic DVT events, and subclassified by proximal DVT and distal DVT.

3.3.3 Secondary Safety Outcomes

Bleeding Complications

Bleeding complications are a composite endpoint previously defined in the literature that includes, 1) symptomatic bleeding into a critical area or organ, 2) bleeding causing a drop in hemoglobin level of 2 g/dL or more over a 24-hour period, or leading to transfusion of two or more units of whole blood or red cells or; 3) bleeding requiring reoperation.

Wound Complications

Wound complications include wound drainage, hematoma, or seroma of an orthopaedic injury that requires a subsequent surgery.

Deep Surgical Site Infection

Deep surgical site infection is defined based on the Centers for Disease Control and Prevention's National Healthcare Safety Network criteria for deep or organ space infections at the fracture site and requires surgical treatment.

3.3.4 Tertiary Outcomes

The following outcomes will be assessed to address the study's secondary aims:

- Patient medication satisfaction will be measured using the Treatment Satisfaction Questionnaire for Medication (TSQM).[31] The 14 item TSQM was developed and

validated by Akinson and colleagues and effectively measures patient satisfaction with various medications. TSQM domains include side effects, effectiveness, and convenience, which sum to a single measure of the patient's medication-related experience satisfaction.

- Direct out of pocket medication cost to the patients related to the blood clot medicines as reported at the final follow up visit

4. STUDY OVERVIEW

The proposed study is a pragmatic multi-center, prospective, randomized trial of 30 mg of subcutaneous low molecular weight heparin/enoxaparin (LMWH) administered twice daily versus 81 mg of enteral aspirin (ASA) taken twice daily in orthopaedic trauma patients. Treatment will be initiated during the initial hospitalization for injury, and will continue for the duration of time the patient is prescribed prophylactic clot prevention medication, per the standard of care at the treating facility. Patients will be followed for 3 months following date of randomization to the trauma center to assess for death, rehospitalization, or complication which occurred between discharge and follow up. At this time, satisfaction, adherence and out of pocket costs will also be reported.

5. STUDY POPULATION

5.1 Description of the Study Population

Approximately 12,200 participants (6,100 per treatment arm) will be enrolled from participating METRC centers over a 42-month period. Participants will be recruited as soon as the decision to place them on prophylactic clot prevention medication is made at the initial hospitalization for their injuries. Consenting procedures are described in detail in Section 6 of this protocol.

5.1.1 Participant Inclusion Criteria

1. Does the patient have a planned operative or non-operative pelvis or acetabular fracture, or any operative extremity fracture proximal to the metatarsals/carpals?
2. Is the patient at increased risk of blood clot(s) from their orthopaedic injury(ies) and will receive a prophylactic blood thinner regimen per standard of care?
3. Is the patient 18 years or older?

5.1.2 Participant Exclusion criteria

1. Did the patient present to the hospital more than 48 hours post injury?
2. Has the patient received more than 2 doses of LMWH or Aspirin for initial prophylaxis?

3. Is the patient on long term blood thinners (other than low-dose aspirin or platelet inhibitors such as Plavix or Aggrenox)?
4. Did the patient have a VTE within the last 6 months?
5. Is the patient on therapeutic (as opposed to prophylactic) blood thinners for an acute issue at the time of admission?
6. Does the patient have a newly diagnosed indication for therapeutic blood thinners (for example vascular injury) that will require therapeutic anticoagulation for more than one week?
7. Does the patient have an allergy to aspirin, or NSAIDs, or a history of heparin induced thrombocytopenia, or other medical contraindication to blood thinners (e.g. peptic ulceration, gastrointestinal bleeding, etc)?
8. Is the patient on higher dose aspirin (>81 mg once a day or higher) for medical reasons or will be treated with higher dose aspirin?
9. Does the patient have underlying chronic clotting disorders (i.e. Factor V Leiden, hemophilia, Protein C and S deficiency) that require full dose anticoagulation or are a contraindication to VTE chemoprophylaxis?
10. Does the patient have end stage renal disease, or impaired creatinine clearance <30 ml/min at time of randomization?
11. Is the patient pregnant or lactating?
12. Does the patient speak neither English nor Spanish?
13. Is the patient is a prisoner?
14. Is the patient is likely to have severe problems maintaining follow-up?
15. Is the patient, based upon the clinical judgment of the treating clinician, NOT equally suited for treatment with either Aspirin or Lovenox?
16. Should the patient be excluded for other reasons at the discretion of the treating physician?
17. Does the patient have a known COVID-19 diagnosis prior to fracture treatment or within 3 months of the index fracture?

Due to the acute nature of injuries experienced by the trauma patient population, some patients may have conditions or treatment plans that are unknown at the time of enrollment that, but when discovered later causes them to become ineligible. Patients who are enrolled and later meet an exclusion criterion that was present but undiagnosed at the time of enrollment will be withdrawn and considered a late ineligible participant.

5.1.3 Co-Enrollment Guidelines

Patients may be co-enrolled into this and other studies, depending on the practices of the local IRB. Co-enrollment must be documented, and event reporting for either study must be reported for both projects.

6. STUDY PROCEDURES

6.1 Screening and Enrollment

6.1.1 Screening

All patients 18 years of age and older with an orthopaedic injury and for whom prophylactic clot prevention medication is indicated will be screened for eligibility at each site by the local Research Coordinator in close collaboration with the surgeon investigators. In this study, it will be important to enroll patients soon after admission to ensure study medication can commence in a timely manner.

Screening will take place either in the hospital or remotely by a Research Coordinator depending on access available to hospital facilities. Remote screening will involve communication between Advanced Practice Providers and a member of the study team in order to document all eligible patients even when the Research Coordinator is not physically at the site. Patients screening status will be logged using REDCap website and either randomized, when eligible, or excluded as an ineligible patient.

A partial HIPAA Waiver will be requested for the purposes of screening for enrollment. The study team will discuss all participants meeting inclusion criteria, and complete and submit a screening case report form (CRF) on every potentially eligible participant. The medical record will be reviewed to assess for exclusion criteria, and the results will be entered into REDCap, the METRC electronic data capture system, in order to document screen failures. The study PI will be available via text or email to answer questions regarding study eligibility. This service will be active during regular east and west coast business hours. When the study PI is not available, this coverage will be provided by a designated co-investigator. Contact information for the PI and alternate contact is available in Appendix A.

6.1.2 Consent and Enrollment

In-person consent:
Once eligibility has been confirmed, the informed consent process will be completed by the Research Coordinator and/or a clinician certified to participate in this study. Eligible study participants or their legally authorized representative (LAR) will be approached as soon as they are able to give consent, and may be enrolled in the study through the time that the first two doses of anticoagulation therapy are administered; i.e. they may receive 2 doses of SOC (as defined by the center) therapy prior to randomization and initiation of the study-directed medication. Individual sites will develop local procedures that will ensure these requirements can be met. Patients and their families may be provided with a pamphlet (Attachment C) describing

the study, the risks and benefits of participation and what will be expected of them if they choose to participate. A video (Attachment D) describing the study treatment and procedures may be provided to assist with the recruitment process. If a patient is unable to consent before 2 doses of SOC anticoagulation therapy are administered and there is no LAR available, the patient will not be eligible for study participation and will be recorded as such. Consent will be obtained in accordance with principles of GCP and ICH guidelines.

Tele or remote consent:
When the Research Coordinator is unable to access the site tele or remote consenting process will be completed by the Research Coordinator in collaboration with an Advanced Practice Provider. Once eligibility is confirmed, the Advance Practice Provider will approach the participant or LAR to provide information on the study, a physical copy of the consent form and an opportunity to be contacted by phone or video call from the Research Coordinator. Once notified, Research Coordinator will contact all willing participants or their LAR and provide additional information about the study and also offer to send a link to the patient recruitment video (Attachment D) for the participant/LAR to view on a personal device. The Research Coordinator will offer to answer questions or put the participant in contact with the treating Physician when necessary. The participant will be offered the opportunity to consult with any family members or friends prior to making a decision on consenting into the study. Consent will be obtained over the phone or video call and documented by the Research Coordinator.

Remote review of consent will not change the requirement for written consent to be documented, unless local regulations relax those requirements for the duration of the COVID-19 pandemic response.

A prototype consent has been prepared for this study (Attachment A) and individual sites may add material but may not delete material thought to be necessary for informed consent. Clinical sites may reformat and reword information to conform to their local requirements. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the signed consent forms will be given to the patient, and this fact will be documented in the patient's record. Once the patient is enrolled into the study they may receive a card/key chain (Attachment E) for study identification and to prompt adherence to the study assigned treatment.

All study materials will be provided in English and/or Spanish as appropriate.

Following completion of informed consent, the participant information will be entered into REDCap where a study number will be assigned, final eligibility criteria confirmed, and the participant will be randomized to a treatment group.

6.1.3 Assessing Capacity to Consent and Consenting a Proxy Respondent

The research staff will endeavor to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol. After introducing the study and reviewing the consent form, the research coordinator will pose several questions assessing the participant's comprehension of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation. The Research Coordinator will ask the questions and determine the appropriateness of the responses. If the Research Coordinator is at all unsure about the patient's ability to consent s/he will consult with the study site PI.

By virtue of the types of injuries studied (resulting from high energy mechanisms such as high speed motor vehicle crashes, high falls, and blast injuries) it is expected that we will have patients with an associated traumatic brain injury which may render them unable to provide consent for the study. Other patients may remain intubated for some time due to lung issues or other reasons related to their trauma. It will be important not to exclude these patients from the study, as it would significantly reduce our ability to produce generalizable knowledge. These patients are at no greater risk of adverse consequences by virtue of their participation in the study, and should be given the same opportunity to participate.

A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if one of the following is true:

- The patient is unresponsive or intubated (and likely to remain unresponsive or intubated during the enrollment window for the study).
- The patient cannot adequately answer at least 2 questions regarding study participation or it is determined that the patient's level of cognition is not likely to change before study medication can be initiated.

The choice of LAR will follow standard procedures and be any of the following: Legal guardian, Proxy (health care agent) named in an advance directive or durable power of attorney for health care; or Family member or other surrogate identified by the state law on health care decisions.

Guidance will be provided to assist the LAR in making the consent decision. They will be advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values and a willingness to administer the study medication, if the patient is still unable to consent at the time of discharge. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

Recognizing that consent is an ongoing process, the study team will continue to assess the participant for their ability to provide consent, and at the earliest possible time, will obtain informed consent from the patient him or herself. Similarly, any participant may withdraw consent at any time during participation in this study.

6.1.4 Informed Consent Process or Assent (for a minor)

N/A

6.2 Baseline Data Collection

Once consent is obtained, baseline data regarding participant characteristics, injury characteristics, fracture classification, medical history/co-morbidities and The Adherence Estimator,[33,34] a brief questionnaire assessing the patient's view of prescription medication use will be collected and entered into the METRC custom version of the REDCap data collection system. Characteristics about hospital course and treatment received will also be collected. A brief interview will be conducted with the participant or his/her surrogate.

6.2.1 Medical Record Review

For all enrolled participants, data related to the index hospitalization will be collected. This will include a daily check of the medication administration record to ensure that the patient is receiving the study drug to which he/she was assigned and to document adherence. If treatment is stopped, held or changed the research team member will either identify the reason for change from the chart or by asking the primary team if the reason is not documented. Other data to be collected includes orthopaedic and other injury characteristics, admission labs, and complications, including a fatal bleed, >= 2 g/dL drop in hemoglobin, reoperation for hematoma evacuation or surgical site infection, other clinically significant bleeding or infectious complication, VTE, PE, and any imaging studies (and results) conducted for bleeding or VTE concerns. Information on the administration of a limited number of concomitant medications with known potential for bleeding side effects will also be collected, including Plavix, or other platelet inhibitors, aspirin, NSAIDs (e.g. toradol, ibuprofen), and any administration of a full dose of anticoagulation medication, as well as the reason, will be recorded.

Due to the potential affects that COVID-19 has on patients, ie increased risk of clotting, COVID-19 status will be recorded if available via medical record review during the index hospitalization and at follow up. Research team member will record whether the patient is experiencing any symptoms related to COVID-19 or has tested positive. Patients who have tested positive during the index hospitalization will be excluded from the study. Patients who test positive between discharge from the index hospitalization and follow up will remain in the study with data collection of COVID-19 status in the case report form. These data will also be retrospectively collected on all patients who have enrolled into the study since January 2020.

6.2.2 Clinical Assessment

No additional clinical assessments will be conducted as part of this study.

6.3.3 Participant Interview

Participants, or their proxies, will complete a brief baseline data, including age, race, history of tobacco, medical history, including history of VTE, peptic ulcer, DM, or cancer, or if they are immunosuppressed, in addition to use of home OCP/estrogen, Plavix, or daily aspirin. The patient will also be asked to assess their views on prescription medication via The Adherence Estimator questionnaire.[33,34]

6.3 Participant Follow up and Data Collection

6.3.1 Follow-up Visit Schedule

Each participant will receive a weekly check in via phone call, text message, mobile application or email by an automated computerized system, Twilio, which will be administered centrally from the data coordinating center at Johns Hopkins. Each participant will also have the option of mailing in a pre-addressed, pre-stamped post card documenting adherence using provided by the study team (Attachment F). Each week, participants will respond to a series of questions, that contain questions from The Brief Medication Quesitonnaire,[32] with automated responses designed to assess adherence to study assigned medication, potential medication crossover and use of other blood clot prophylaxis. At the time of this contact, if a participant is found to no longer be taking prophylaxis for any reason other than discontinuation by the treating physician, the participant will receive a message that he/she is at increased risk of blood clot due to his/her injury experience, and should contact his/her surgeon to determine whether or not continued prophylaxis is still indicated (Attachment B). If the patient does not respond to two subsequent surveys they will be contacted by a representative from the coordinating center. The automated contact will stop when the participant responds that prophylaxis is no longer indicated or at the time of the 3 month follow-up visit, whichever comes first.
Participants may opt out of this contact at the time of enrollment or any time during the follow up period.

All outcomes in this study will be assessed at 90 days (3 months) post randomization, and all efforts will be made to ascertain outcomes at this point in time. Because this is a pragmatic study and there are no study visits, participants will also complete a visit which will coincide with a regularly scheduled standard of care follow-up visit approximately 3 months post randomization at which point study outcomes will be assessed. If participants are unable to return to the clinic they may be contacted to complete the 3 month follow up visit via phone call, email, or mail. If a patient completes the follow up visit prior to the 3 month anniversary, a medical record review will be conducted in order to assess for potential outcomes that were not recorded at the premature follow up visit. To fully assess for any missed outcomes, the research coordinator may assess for potential events in the patient's medical record..

At the time of the 3 month follow up visit (in-person or virtual), participants will be interviewed by the Research Coordinator to assess for the occurrence of any clinical outcomes, including VTE events or complications secondary to treatment since their hospitalization. For each event identified, the participant will fill out a release of information form that will allow the research staff to obtain records related to the event, if they occurred outside the index facility. Participants

will be asked about study medication satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM)[31] and about their total out of pockets costs related to obtaining the study assigned medication. Additionally, the medical record will be carefully reviewed to assess for any complications treated at the index facility, including in the clinic, ED, or resulting in a rehospitalization.

As stated above, due to the potential affects that COVID-19 has on patients, ie increased risk of clotting, COVID-19 status will be recorded if available via medical record review also at follow up. Research team member will record whether the patient is experiencing any symptoms related to COVID-19 or has tested positive. This data will be collected on all patients who have enrolled into the study since January 2020.

Lost to follow up participants

A percentage of participants will fall in the category where they cannot be contacted, do not return to clinic, or return to clinic but do not have 90 days of follow-up. Additional contact methods will be used to verify these participants' death status which is critical for determining the primary outcome, all-cause mortality. The following methods, which are also described in more detail below, will be used to assess outcomes on these individuals: (1) medical record review, (2) postcard questionnaire, (3) phone call or text follow up from coordinator (4) search via LexisNexis Accurint system, (5) phone call and text message follow up from MCC, (6) search via Limited Access Death Master File (LADMF)

Medical Record Review

If the participant cannot be contacted and does not return for a final research visit, medical records will be abstracted through the last orthopaedic encounter occurring between anytime from the last clinical encounter to the time of medical record review. The visit occurring closest to the 3 month follow-up target should be recorded(e.g. for a participant seen at 60 days, 185 days and 400 days, the 60 day visit should be recorded to demonstrate use of services in the follow-up interval, and the 185 day visit should be recorded to demonstrate that the participant was alive and free of any orthopaedic events at 185 days and therefore also alive and event-free at 90 days, the date of interest. No other visit data should be recorded. Attempts will be made to obtain medical records or autopsy reports for all participants who are discovered to be deceased at the time of the follow up visit. If the participant died at home, family members will be asked to provide a cause of death, if known. No attempts will be made to follow up with family, and the deaths will be recorded as "unknown" cause.

If a patient cannot be contacted AND has no evidence of returning for any orthopaedic clinical visit, the medical record will be searched for any evidence of an encounter with the medical system documenting that the patient survived through at least 3 months post randomization. If the encounter occurred before 3 month post randomization information, information related to study outcomes available at the encounter. If the encounter occurs anytime following the 3 month post randomization date the date and visit type will be recorded. The resulting information

will provide evidence that the patient was alive during the window of interest, allowing ascertainment of information on the primary outcome.

Postcard questionnaire

Each lost to follow up participant will receive a one-time pre-stamped postcard questionnaire requesting information on the participant's death status. The postcard will be addressed to the participant however may be returned by a family member, friend, or resident of the participant's home. Sample of this postcard is in Attachment H.

To facilitate centralized distribution and retrieval of these cards, clinical sites will send the patient's full name and mailing address, along with the study ID number, to the MCC using a secure, encrypted, password-protected File Transfer Protocol. The MCC will centrally send out postcards using an automated postcard development and mailing electronic service.

Phone call/text message follow up (Research Coordinator)

Research coordinators will call the participant or emergency contact listed in the participant's medical record or social work/case management file to determine the participant's death status. This phone call will be in addition to any attempts made during the follow up period. If the Research Coordinator gets in contact with the patient a full follow up visit and questionnaire will be conducted. If the Research Coordinator can only determine the participant's death status based on conversations with the family and/or emergency contact the death status will be recorded. Sample of the text message/call script is in Attachment I.

Search via LexisNexis Accurint Services

The MCC will obtain identifiers such as but not limited to the patient's name, date of birth, social security number, and last known address using a secure, encrypted, password-protected File Transfer Protocol. The identifier will be used to conduct probabilistic mapping through public and proprietary database search. Any identifiers will aid in specialized mapping of this database will be used in the search, and the database will return up to date mailing and phone contact information for the participant, as well as any publicly reported deaths.

Phone call/text message follow up (Centralized through MCC)

The MCC will centrally contact each participant and emergency contact, when necessary to evaluate the death status of the participant using the contact phone numbers previously provided by participating centers for weekly follow up as well as information obtained from the Accurint search. Clinical sites may also obtain any additional phone numbers associated with the participant's medical record and transfer it, along with the study ID number, to the MCC using a secure, encrypted, password-protected File Transfer Protocol. All statues will be saved in REDCap. Sample of the text message/call script is in Attachment I.

Search via Limited Access Death Master File (LADMF)

There will be a subset of patients who cannot be contacted AND have no evidence of any further encounters with the clinical system. For these cases, ascertaining final death status is critical to the validity of the study, and the study team has developed a plan to allow sites to obtain this information while conforming to local policies regarding the sharing of PHI and accessing available data. Because this study is being executed in 21 trauma centers, including 2 centers in Canada, the method for determining if a patient passed away during the study interval will vary. Local IRBs will review the protocol and make a determination regarding if and how this information will be obtained, according to the following options:

A. Sites have the option to send a secure, encrypted password-protected LOOK-UP File to the MCC for a centralized database search of the Limited Access Death Master File (LADMF).

B. Sites have the option to locally and independently access the LADMF or local death record database, including Canadian sites, to conduct a search of patients.

C. Sites are unable to access the LADMF either locally or send data for a centralized search and therefore opt out of obtaining this information for their patients.

Option A: Established by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) the LADMF is a centralized database of death record information of all state vital statistics offices. The LADMF requires at least one of the following identifiers: name, date of birth, and social security number to obtain accurate information. Consequently, for each patient completely lost to follow up, clinical sites may obtain the patient's social security number from the hospital billing record and transfer it, along with the study ID number, patient name, and date of birth to the MCC using a secure, encrypted, password-protected File Transfer Protocol. The MCC will link these data with the Social Security Administration Death Master File to determine if a death has been registered for the study patient. Only the study ID and death status for the patient will then be linked to the study database.

A HIPAA waiver will be sought to cover the exchange of PHI between institutions for patients whose death status is unknown to determine the primary outcome on patients who are lost to follow up. The data obtained for this purpose will saved in a separate LOOK-UP file and will not be linked to contact data or identifiable data of the study dataset.

The MCC may access the patient's SSN and develop a LOOK-UP File for all those individuals identified as loss to follow up with unknown death status. This LOOK-UP File contain information needed to conduct a search on the LADMF (may include: name, date of birth, SSN). A HIPAA waiver will be sought to share this information for the purposes of obtaining death status on every patient who is lost to follow up with no indication of the status of this outcome.

Waiver of Consent. We are requesting a waiver of consent for accessing identifiable data. We believe that we meet the Code of Federal Regulations criteria for a waiver of consent as follows:

Can informed consent be waived or consent elements be altered under 45 CFR 46.116(d)

a. **The research involves minimum risk to subjects:** Yes, the research will involve existing data

b. **The waiver or alteration will not adversely affect the rights and welfare of the participants:** Yes, the data currently exist and will only be used for the search and determination of status. The analysis will be conducted using de-identified data with additional data will be collected, nor will any procedures be performed as part of the proposed analysis.

c. **The research could not practicably be carried out without the alteration or waiver:** Yes. The cases where the patient is lost to follow up would not allow for an opportunity to obtain consent.

d. **Whenever appropriate, the subject will be given additional information about the research after it is completed:** Yes. Study results will be posted on a study website.

Option B: For sites that will conduct a search locally will obtain an account to and search the LADMF or a different local death record database independent of the MCC. The results of each patient's primary outcome status will be recorded in the patient case report form. Sites are permitted to use a local death record centralized databased in addition to or instead of the LADMF to obtain final death status on lost to follow up patients.

Option C: For sites that will not conduct a search either locally or centrally through the MCC will not obtain the primary outcome on these patients and those data will be considered missing.

6.3.2 Retention

Every effort will be made to retain participants in the study. The study participants will receive an honorarium in recognition of their time and effort. $20 will be given for completing the **3** month visit in appreciation for their time and effort. Participants who complete follow-up activities by phone or email will be given $20 for competing the interview. We will also keep participants engaged through use of study updates on the study webpage and distribution of follow-up reminders, which can include mailings and e-mails.

7. STUDY TREATMENTS

Patients meeting inclusion/exclusion criteria will be prospectively randomized to one of two treatment arms using the REDCap Database randomization tool embedded. Block randomization with variable block sizes will be used.

7.1 Study Treatments

7.1.1 Description of treatment

Study Treatment 1: LMWH is currently an accepted medication used to prevent blood clots after trauma, and it is supported by existing guidelines so it is already in widespread use through the United States.[9,10] Enoxaparin is available from multiple manufacturers; local site purchasing will determine the product received by the patient. Clear guidelines already exist regarding dosing in very obese patients as well as in patients with renal disease.[35,36] The LMWH intervention is expected to be 30 mg enoxaparin SC twice a day which is already standard in many trauma hospitals. The protocol for this pragmatic trial will allow for variations in dosing, per the standard of care at sites, as needed for patients who are very obese or exhibit renal dysfunction. These variances will be recorded to allow them to be identified in the data.

Study Treatment 2: Aspirin is currently regarded as an accepted medication to prevent blood clots after orthopaedic surgery, is supported by existing guidelines[37] and is already in widespread use in the United States. Aspirin is less commonly used in trauma although it has gained significant popularity in the orthopaedic arthroplasty (joint replacement) domain.[22,23,27] Aspirin was chosen as the comparative intervention because it is thought to have an excellent complication profile (low rates of bleeding and chronic wound drainage) and still to be effective in preventing blood clots in the lung, although these data are in joint replacement patients.[22,23,27,37] Aspirin works by effecting platelets irreversibly and this effect typically lasts 7 days, which is a potentially important difference from the shorter acting LMWH. The advantage of a shorter acting medication is that the effect can be turned off easily when the patient needs additional surgery or if a contraindication for bleeding develops. A down side is that missed doses with LMWH quickly place the patient with no blood clot prevention. Aspirin is typically continued even when surgeries are performed so the fact that aspirin cannot be "reversed" is likely not important in this domain, but the importance of this effect in trauma patients is unknown.

The dose of aspirin for this study is not obvious as several reported doses have been used successfully. Options include 81 mg once a day, 81 mg twice a day, 180 mg once a day, 325 mg once a day, and 325 mg twice a day. The desired effect of reducing the risk of clots is thought to occur at the 81 mg dose once a day and many joint replacement surgeons use this dose to prevent blood clots.[38] Anti-inflammatory effects are thought to become more pronounced as the dose increases and some of the original joint replacement studies used 325 mg twice a day. We believe that lower doses may be desirable in trauma as it likely reduces the chance of bleeding from other traumatic injuries and it is not necessarily desirable to have the anti-inflammatory effects of higher doses, as anti-inflammatory medicines have been linked to delayed bone healing in animal models.[39] We therefore have chosen 81 mg twice a day as it represents a dose towards the lower end of the dosing spectrum and gives twice a day dosing, similar to LMWH, decreasing the chance of patients missing a dose for the whole day. Further, a study of geriatric hip fractures,[21] which is as close to our population as has been studied for this question, successfully used 160 mg once a day.

7.1.2 Investigational Drug Status

Both study treatments are FDA approved medications that are commonly used for the indication proposed in this application; however only LMWH has this listed as an approved indication in its product labelling. ASA for this indication is "off label" for use as DVT prophylaxis. In accordance with 21 CFR 312.2, this study meets IND Exemption requirements. An application for an IND exemption was approved by the FDA for the proposed indications outlined in this protocol. The intention of the protocol is not to support a new indication for use or significant change in labeling of the drugs; is not intended to support a change in advertising for the drugs; will not test a new route of administration or dosage of the drug, nor is it being used in a new clinical population; and the study will be conducted with informed consent and in compliance with 21 CFR 312.7 regarding promotion and sale of drugs. Patients in the study will be actively monitored for any adverse reactions.

For patients enrolled at Canadian sites, the in-patient administration of ASA and the ASA prescribed to the study participant at their discharge will be dispensed by the treating hospital's pharmacy. As per the labelling standards of the Food and Drug Regulations (C.05.011) labels for the ASA, in both English and French, will be included with each administered dose. The label will state that the ASA is for clinical trial use only, the name and identifying mark of the drug, the expiration date of the drug, the recommended storage conditions for the drug, the lot number for the drug, the protocol code "PREVENT CLOT", and the name of the sponsor (R Adams Cowley Shock Trauma Center, University of Maryland, 22 Greene St., 3rd Floor, Baltimore, MD, 21201).

7.2 Assessment of Participant Adherence with Study Agent(s)/Intervention(s)

Adherence to study medications and out of pocket costs will be assessed at the 3 month follow up visit, including assessing for any potential occurrence of treatment crossover.

If participants do not return for the 3 month study visit, they will be contacted by the study research coordinator by phone, mail and/or email. The participant will be asked to return to the clinic for a follow-up appointment. If the participant is unwilling to return, follow up information will be collected by phone or via an email survey assessing for adherence and study outcomes.

7.3 Precautionary and Prohibited Medications and Procedures

In this trial, participants will be randomized to receive either LMWH or aspirin. Participants in this study may not receive any other full dose medication as prophylaxis for anticoagulation or as treatment for a VTE even, nor may they receive additional dosages of aspirin above 81 mg daily. There are no other prohibitions regarding medications management, and participants will be treated according to the local standard of care. Data on specific concomitant medications will be collected (See Section 6.2.1). Should it be determined that the medication the participant was randomized to is no longer clinically appropriate, the study medication will be stopped, the

research team will record the reason for medication discontinuation, and the participant will continue to be followed through the 3 month follow up.

7.4 Rescue Medications

Any need for rescue medication resulting from a drug overdose or sensitivity will be handled per the standard of care at the treating institution or where the patient seeks care.

8. ASSESSMENT OF SAFETY

The study will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. The approach to defining and reporting events is based on the 2009 FDA Guidance for Clinical Investigators, Sponsors, and IRBs on adverse event reporting to IRBs (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf)

The medical monitor (MM) is responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of Serious Adverse Event reports; resolving safety issues; and interacting with Principal Investigators.
Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.1 Definitions

8.1.1 Adverse event

Any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject's participation in the study, whether or not considered related to the subject's participation. Several adverse events, or complications, will be collected as primary and secondary outcomes of the study. The most severe of these events include: (1) Death, (2) Fatal bleeding into a critical organ (retroperitoneal, intracranial, intraocular, intraspinal); (3) Significant/massive PE central pulmonary embolism with resulting heart strain (PE); (4) Wound drainage or hematoma requiring reoperation; (5) Wound drainage, bleeding or hematoma that does not require reoperation; (6) Bleeding event that requires intervention (e.g. chest tube, interventional radiology embolization); (7) Surgical Site Infection requiring reoperation; (7/8) Surgical site infection that does no lead to reoperation but requiring antibiotic treatment; (9) Greater that 2 mg/dL drop in hemoglobin within 24 hrs; and (10) GI Bleed. These and other

complications common in the trauma population will be reviewed in aggregate twice annually by the DSMB to assess for differences between treatment groups. They will be reported to the IRB on an annual basis, unless they meet the criteria for Serious Adverse Event (see below).

8.1.2 Unanticipated problem

Any incident, experience, or outcome that meets all of the following criteria:

(1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the study.

(2) is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments.

(3) suggests that the participation in the study may place subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Please note that not all adverse events are unanticipated problems and only some unanticipated problems are in fact adverse events. For instance, if a laptop containing study data is stolen, this is an unanticipated problem but it is not an adverse event since it is not an untoward or unfavorable medical occurrence in a human subject

8.1.3 Serious Adverse Event

A serious adverse event is defined as:

1. Unanticipated events possibly related to exposure to study medications such as angioedema, agranulocytosis, hepatic injury, or Stevens Johnson syndrome
2. Other events that are serious AND either related or possibly related to the study which occur at a higher rate than expected in this population
3. Other events that are unexpected AND serious AND either related or possibly related to the study beyond the complications expected in this population

Note that deaths are an expected outcome in this population, and will not be reported as serious adverse events, unless they are determined to be related to study treatment and occur at higher than expected rates in the study population.

8.2 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

8.2.1 Methods and Timing of Assessment

Adverse events (complications) may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits. Adverse events will be assessed for during the index hospitalization and at the 3 month study visit. They will be recorded on study data forms with an indication of whether or not they are thought to be associated with participation in the study.

8.2.2 AE/SAE Grading and Relationship Assignment

Adverse event grading: Adverse events will be graded using standard criteria. Relationship of event to the study procedure will be determined by the study physician.

GRADE 1 (Mild) Transient or mild discomfort (< 48 hours); no medical intervention/therapy required

GRADE 2 (Moderate) Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 (Severe) Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 (Life-threatening) Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Relationship Assignment The relationship of the adverse event to participation in the study will be assessed as either:

Definitely related
Probably related
Possibly related
Unlikely related
Unrelated

8.2.2.1 Adverse Events related to study medications.

The study will capture safety information on LMWH and aspirin, both of which are licensed by the FDA. Complications will be classified as study outcomes (8.1.1), and their relatedness to medication exposure will be assessed by the treating physician**.**

8.2.3 Recording and Documentation

Sites will maintain source documents including but not limited to laboratory and radiology reports, clinical notes and discharge summaries. After review of initial and final reports by the medical monitor, the events may be reclassified at their discretion.

8.2.4. Management of Adverse Events

Adverse Events and Serious Adverse Events will be managed according the medical judgment of the treating physician.

8.3 Adverse Event Reporting Procedures

8.3.1 Local Reporting Requirements.

Study sites must always follow and comply with their own local institution's adverse event reporting requirements. Depending on the local requirements, a site may report events locally and not report those events to the METRC Coordinating Center. Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.3.2 SAE and Unanticipated Problem Reporting Requirements

All Serious Adverse Events that are unexpected AND related or possibly related to the study must be reported to the Medical Monitor and METRC Coordinating Center within 72 hours of being made aware of the event. The MM will review the event within 48 hours of receiving notice of the event, and will make a determination of relatedness as well as the required action (stopping medication, informing other sites, etc). When necessary, the MM may convene the DSMB to discuss an event.

In addition, Unanticipated Problems (UPs) that are not adverse events must also be reported to the METRC Coordinating Center within 14 calendar days after the event has been discovered. SAEs/UPs will be reported to the METRC Coordinating Center by entering the SAE/UP form into REDCAP. REDCap is programmed to automatically send an email to the Coordinating Center for both SAEs and UPs, and to the Medical Monitor in the case of an SAE.

The Medical Monitor for this study is:
Gregory Vercellotti, MD, FACP
University of Minnesota
Division of Hematology, Oncology and Transplantation
420 Delaware Street SE
Minneapolis, MN 55455
Telephone: 612-624-5620 Fax: 612-625-6919
Email: verce001@umn.edu

LMWH and aspirin are available from multiple sources and have generic versions available so consequently there will be variability in manufacturer.

8.3.3 METRC Coordinating Center Reporting Responsibilities

When an event is determined to be unexpected and related to study medication exposure, the Coordinating Center will send a copy of each report received about the event to all clinical sites, with instructions for each to forward the report to their IRB.

Copies of the report will also be sent to the Study PI, and to the DSMB. The MCC will maintain a list of such events for reporting and review at DSMB and Steering Committee meetings.

8.4 Reporting Pregnancy (Replace text with "N/A" if not applicable)

Pregnancy will always be captured on case report forms as a medical event**.** LMWH is considered a category "B" medication – to be used only if clearly needed. Aspirin is considered a category "D" medication – adverse reactions have been found in humans – but only in the third trimester, and no participant who is not pregnant at the time of enrollment will still be on study drugs by the final trimester of the pregnancy. If a woman becomes pregnant while on the study medication, the decision to continue study medication will be made by the local treating physician, and the event will be reported in an Unexpected Event Form. Regardless of whether the medication is discontinued or not, the patient will remain in follow-up until the follow-up period is completed and a report on the outcome will be submitted.

8.5 Type and Duration of the Follow-up of Participants After Adverse Events

Study patients who experience an SAE will be followed until resolution of the event, and a final report will be submitted to the medical monitor, the coordinating center and the pharmaceutical company (if applicable).

8.6 Stopping Rules

The DSMB will review the overall progress of the trial in terms of recruitment, data quality, and event frequency and makes a formal recommendation to PCORI at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications or be stopped.

There are two formal interim analyses and one final analysis planned to assess differences between group with respect to death within 90 days of randomization. The first will occur after one-third of enrolled patients are followed for 3 months. The second will occur after two-thirds of enrolled patients are followed for 3 months. At each interim analysis, the DSMB will evaluate whether there is a difference in mortality rates between groups. Specifically, they will assess whether the absolute difference in the risk of death between aspirin and LMWH is different than zero. At each interim analysis, two-sided confidence intervals for the difference in risk for death will be computed. The overall type I error of the interim monitoring procedure will be controlled by using a 99.6% confidence interval at the first interim analysis, 98.8% confidence interval at the second interim analysis and a 96.2% at the final analysis. If probability of dying is 1% in both arms, the probability of falsely declaring harm using this procedure is less than 5%.

8.7 Premature Withdrawal of a Participant

A participant may be withdrawn from the study without consent if the sponsor decides to end the study. Other reasons for removing a participant without consent may include but are not limited to non-adherence with the protocol and/or therapy, inappropriate behavior towards study personnel, and incarceration.

8.8 Replacement of a Participant Who Discontinues Study Treatment

Participants who are withdrawn from the study will not count towards the total sample size accrual and will be replaced. Participants who are lost to follow up and have unknown treatment or outcome status will be counted as lost and will not be replaced.

9. MONITORING

9.1 Site Monitoring Plan

The METRC Coordinating Center will be responsible for site monitoring consistent with ICH/FDA guidelines. Monitoring will include a combination of remote and on-site visits of participating clinical research sites to review the individual subject records, including consent forms, case report forms, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. During the site certification process, the monitors also use remote methods to inspect sites' regulatory files to ensure that regulatory requirements are being followed.

The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, or other regulatory authorities for confirmation of the study data.

9.2 Safety Monitoring Plan

9.2.1 Safety Review Plan by the DSMB

An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality. Two interim analyses will occur, the first after 1/3 patients are at 3 months from enrollment and the second after 2/3 of the patients are at 3 months from enrollment

The DSMB is a multidisciplinary group with a written charge provided by METRC. The DSMB will meet in person to review the protocol. After the trial commences, the DSMB meets twice a year to review data or other issues. The DSMB may request more frequent meetings if necessary, to fulfill it charge. It may also request additional safety reports on a more frequent basis. For

example, all serious adverse events (SAE) are reported to the DSMB for their consideration and recommendations as they occur.

At its first meeting the DSMB will review definition of all outcomes, adverse events and serious adverse events and revisions to the protocol made as appropriate. Summary data on adverse events (together with study outcomes) will be monitored by the DSMB at its semiannual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events (complications) by masked treatment group, by clinic, or in other subgroups requested by the DSMB.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events (complications) and serious adverse events, for transmission to the IRBs at each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.

The DSMB will review semi-annual reports by masked treatment groups of the primary and secondary outcomes as well as all adverse events that are not identified as outcomes per se.

Interim data on safety measures requested by the DSMB are reviewed at each of the scheduled semi-annual full meetings. Analyses will be prepared comparing rates of adverse events by treatment group, by clinical center or by other subgroups as requested by the DSMB. Serious adverse events will be reviewed by the medical monitor as they occur with the option of a teleconference if any DSMB member requests

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size

The study is well powered to address all of the specific aims. The primary driver of size is specific aim 1, which involves non-inferiority for death. We plan for a sample size of 12,200. Enrollment will continue up to 12,400 to account for the potential removal of post-randomization inappropriate enrollment and late ineligible patients for a total of up to 12,400 to be randomized, but 12,200 included in the final analytic sample.

Our original sample size estimated the baseline rate of PE-related death was 0.25%. A non-inferiority margin of 0.36% was based on the costs and administration benefits of aspirin as calculated from a discrete choice experiment of 232 orthopaedic trauma patients (Haac 2017). Using a noninferiority design, we calculated that a sample size of 12,200 patients would provide more than 95% to show that aspirin was noninferior to LMWH for the prevention of PE-related death. The calculation used an alpha of 2.5% and accounted for two interim analyses and 7.5% attrition.

After changing the primary outcome from PE-related death to all-cause mortality, the estimated baseline rate increased from 0.25% to 1.0%. A non-inferiority margin of 0.75% was based on the patient-important benefits and a survey of experts and orthopaedic surgeons (Haac 2017). Using a noninferiority design, we calculate that a sample size of 12,200 patients would provide more than 95% to show aspirin was noninferior to LMWH in the preventing death. If the probability of death is 1% in the LMWH arm and 1.75% in the aspirin, the study has less than 2.5% chance of declaring non-inferiority.

10.2 Randomization

Patients who provide consent to be enrolled in the study will be randomized electronically by the online Data Management System maintained at the Coordinating Center at the Johns Hopkins School of Public Health. Following consent, a randomization code is provided assigning treatment group and whether or not the participant was selected to be prospectively surveyed regarding out of pocket costs and treatment adherence. Randomization tables are encrypted and will not be shared with study investigators. While this study is not blinded, provision of linkages between randomization codes and treatment assignment will follow existing METRC unblinding SOP. Patients will be randomly assigned (within center) using block randomization with variable block sizes to either LMWH or aspirin. Compliance regarding the proper treatment protocols will be monitored by local Research Coordinators in cooperation with the attending surgeon. Any deviation from the assigned treatment group and the actual treatment received will be recorded.

10.3 Missing Data and Measures to Minimize Bias

Missing data is a serious concern that complicates the interpretation of the study results. For missing baseline data, we will use multiple imputation. We do not expect any missing outcome data for death or clinically significant PE. As with most prospective studies, missing data will be unavoidable, even with excellent follow-up. We will employ the following strategies to address missing data in the design, conduct, analysis and reporting of study results: (1) limit participant burden and inconvenience in data collection, (2) provide compensation for participation and completion in the study; (3) provide pre-study training of investigators and research staff to emphasize the importance of full participation in the study during the consent process (even if the patient is “feeling better”); (3) reimburse study sites based on follow-ups completed rather than on per-patient basis; (4) monitor and report missing data rates during the study and provide on-study reinforcement and support to ensure high follow-up rates; (5) collect information on the reasons for missing data; (6) actively engage participants in the study and educate them about the importance of their participation; and (7) collect surrogate information on participants who miss clinic visits; (8) require sites to go back and fill in missing data using medical record information when applicable; (9) carefully track and collect data on any discontinuations, to include the reasons for discontinuation, who decided that the participant would discontinue; and whether the discontinuation involves some or all types of participation; (10) avoid using single imputation

methods and will employ multiple imputation strategies for handling missing information when necessary; (11) analyze data under a variety of modeling assumptions regarding how strongly the missingness mechanism is related to outcomes; (12) conduct sensitivity analyses to evaluate the robustness of the study results to various untestable assumptions about the missing data mechanism; (13) estimate treatment effects (utilizing relevant auxiliary information) under the missing at random assumption; (14) explore the effect of departures from the missing at random assumption using pattern-mixture and selection modeling techniques; and (14) we will account for all participants who enter the study in the reporting or our results whether or not they are included in the analysis.

10.4 Planned Interim Analysis

As described above, an independent Data and Safety Monitoring Board (DSMB) will monitor interim data as the trial progresses to ensure patient safety, review efficacy, evaluate recruitment, and assess overall data quality. O'Brien-Fleming stopping guidelines for efficacy will apply. The interim analysis will occur twice, once when the first third of patients are enrolled, and then again when two thirds of patients are enrolled, and will look specifically at the risk of death/PE among patients receiving aspirin relative to those receiving LMWH. After reviewing the results, the DSMB will then a formal recommendation as to whether the trial should continue unmodified, continue with protocol modifications, or to be stopped.

10.5 Analysis Plan

10.5.1 Intention to Treat Analysis

Patients will be followed for 3 months post-randomization. The primary statistical analysis will follow the intention-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized. The primary estimand (difference in all-cause mortality between treatment groups) will be estimated using treatment-specific Kaplan-Meier estimators. The other intention-to-treat estimands will be estimated using treatment-specific cumulative incidence function estimators. Formal definitions of the estimands are provided in the *Statistical Analysis Plan*.

We will test the primary outcome for non-inferiority using the upper bound of a two-sided 96.2% confidence interval compared to the pre-specified non-inferiority margin of 0.75%. If non-inferiority is established at our pre-specific non-inferiority margin, we will test for superiority.

Two-sided 95% confidence intervals will also be presented for all other outcomes, but null-hypothesis significance tests will not be performed.

10.5.2 Per-Protocol Analysis

To understand treatment differences in the presence of non-adherence, we will perform a secondary per protocol analysis for the nine estimands. The per protocol estimands will only include the subset of patients classified as protocol adherent, based on the following definition.

1. If the patient is prescribed thromboprophylaxis at discharge, the patient must be discharged on the allocated study medication.
2. The patient must have been adherent for at least 80% of their in-hospital study medication doses.

Dosage changes due to non-medical reasons, protocol crossovers due to non-medical reasons, and patient refusal to continue medication will be considered non-adherence.

To the extent possible, we will adjust for key baseline covariates. Missing baseline covariates will be imputed using multiple imputation.

10.5.3 Subgroup Analysis

We will perform one subgroup analysis to assess the variation in treatment effect for our primary outcome based on patient age, specifically >60 years or age vs. ≤60 years of age. Interaction tests will be performed to assess heterogeneity of treatment effects.

Further analysis details are provided in the *Statistical Analysis Plan*.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

Quality Control (Q/C) and Quality Assurance (Q/A) procedures that apply to all studies are outlined in the METRC Manual of Operations (MOP). A certification process will be used as a basis for training and certification of the study personnel involved in data collection. In addition to consortium wide training and certification procedures, additional requirements may be added based on the nature of the study. Ongoing data edits and audits will be performed to ensure collection of quality data. The continuous and timely flow of data from the centers to the MCC is an essential prerequisite for maintaining data quality.
Monthly enrollment reports will be distributed to each center that will summarize recruitment, data completion and timeliness of data entry. These reports will also include a set of queries generated by REDCap and sites will be asked to address these queries within 10 business days.

11.2 Training and Certification of Centers

All participating centers together with their respective study personnel will undergo certification that included training, local site IRB, and a knowledge assessment on the study design and procedures. This training will include a training for research coordinators in the submission of regulatory documents, data collection procedures, and study follow-up, as well as meetings between the PI, study project director, and the study team at each site to ensure that the procedures are well understood prior to engaging with research subjects.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 IRB/Ethics Committee

IRB approval will be obtained from the MCC at Johns Hopkins Bloomberg School of Public Health, the University of Maryland School of Medicine, and each participating clinical site according to METRC policies and procedures. Sites that recruit patients will submit METRC study recruitment materials to their organization's IRB prior to use at that facility.
Sites must provide the Coordinating Center with a copy of the initial IRB approval notice and subsequent renewals as well as copies of the IRB approved consent statements.
No site can begin work related to this study until the site has been certified by the MCC in accordance with METRC policies and procedures.

12.2 Exclusion of Women, Minorities, and Children (Special Populations)

The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (African-Americans, Asian-Americans and Hispanics) as well as non-Hispanic white subjects.

***The study will not include children or prisoners*.**

12.3 Participant Confidentiality

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission to the Data Coordinating Center.

Patients will be identified in the central data collection system, REDCap only by an identification code but not by their name, SSN, or hospital medical record number. Study Site Investigators will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses available only to local clinic staff certified by the MCC to participate in the study.

The participants who agree to participate in the adherence study will sign a local site-specific HIPAA authorization form allowing their contact information to be shared with the coordinating center so that follow up calls can be made.

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the sponsor (MCC), IRB, or DSMB. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

12.4 Study Discontinuation

Participants will be informed that they may discontinue the study at any time, for any reason. They will be assured that the medical care which they receive at the participating facility will not be affected should they elect to discontinue participation in the study.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Each study site is responsible for collecting and uploading study data in a timely fashion. The research coordinators at each site will obtain the information necessary to complete the electronic case report forms (eCRFs) from several sources including but not limited to, the patient's medical record, clinical evaluations and patient interviews. The Site Research Coordinator will enter non-personally identifiable information into a central /and secured web-based data management system being implemented for all Consortium studies, known as REDCap. This data management system has incorporated state-of-the-art features for electronic data collection and is configured in accordance with best practices for information technology and research data management.

Data related to patient clinical course, as well as baseline characteristics and medication adherence will be collected prospectively by local research teams. Data related to the primary endpoints, pulmonary embolism and death, must be collected and certified by the local study investigators.

All research data, in hard copy or electronic form, will be stored and managed in a secure manner following applicable federal regulations and ICH guidelines and according to institutional policies and practices. Hard copy documents generated by the sites which contain subject data, patient identifiers and contact information will be stored in secure, locked

containers (file cabinets, drawers, etc.) in accordance with standard document management practices.

At all times only MCC-certified key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents, including electronic data and medical records. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct. This information will be available for audit by study monitors and representatives of the local IRB and the MCC.

13.2 Data Capture Methods

Data will be collected in real time by the investigator or study coordinator directly on electronic Case Report Forms (CRFs).

13.3 Types of Data

Data will include: medical and surgical histories, laboratory reports, radiology reports, clinical evaluations, medication administration records, adverse events and patient interviews.

13.4 Source Documents and Access to Source Data/Documents

Source documents laboratory results, patient surveys, medical records, etc. will be maintained at the site and will be made available to study monitors, and representatives of regulatory agencies including the MCC and IRB.

13.5 Study Records Retention

Study records will be maintained in accordance with current ICH guidelines. Data will be maintained for five years following the end of research-related activities, including data cleaning and analysis. At the end of this period, each site will provide the Coordinating Center a signed verification that these data have been destroyed.

13.6 Protocol Deviations

Records of protocol deviations will be noted on the Protocol Deviation CRF (AF05) with the reason for the deviation recorded, as well as any action taken to mitigate the deviation. This information will be entered into REDCap. These records will be provided to the site's IRB in accordance with local reporting requirements and be made available to study monitors.

14. PUBLICATIONS POLICY

Publications will be written in accordance with the METRC publication policy (available on the METRC website: www.metrc.org).

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17. APPENDICES

APPENDIX A: STUDY CONTACT ROSTER

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APPENDIX B: DATA COLLECTION SCHEDULE

Assessment	Baseline	Baseline – 3 months	3 month
CRF00: Inclusion/Exclusion	X		
CRF01: Patient Contact Information	X		
CRF02: Patient Characteristics	X		
Demographics • DOB • Age • Sex • Race • Height • Weight • Tobacco use • Health Insurance • Education • Adherence Estimator			
CRF03: Medical History	X		

• Medications taken Prior to Injury
  ○ OCP or Estrogen use
  ○ Antiplatelet agent
  ○ ASA daily use
  ○ Blood thinners
  ○ NSAIDs (daily use or prescription)
• Co-morbidities
  ○ Charlson Comorbidity Index
  ○ History of VTE, peptic ulcer, DM
  ○ Cancer
  ○ Immunosuppression			

CRF04: Injury Characteristics	X		
• Injury date/time • Circumstances • Type of Injuries (orthopaedic/non-orthopaedic) • Side of Injuries • AO/OTA Fracture classification • Gustilo Classification • Tscherne Classification of Soft Tissue Injuries • Injury Severity Score, TRISS, ICU days, ventilator days, and ICD-9 codes			
CRF05: Index Hospitalization	X		

Assessment	Baseline	Baseline – 3 months	3 month

• Admission date/time
• Discharge date/time
• Discharge outcome (discharged/death)
• Admission labs (if tested)
  o INR
  o PTT
  o Platelets
  o Max serum lactate (first 24 hours)
  o Creatinine
  o TEG parameters (if ordered)
• Surgical data
  o Surgery info (ortho/non-ortho surgeries)
  ▪ Dates
  ▪ Total number of surgeries
  ▪ Weight bearing status on discharge
  o Total number of surgeries (ortho/non-ortho)
• Imaging studies (and results) conducted for bleeding or VTE
  o Angiogram
  o Ventilation perfusion (VQ) scan
  o Duplex scan/ultrasound
  o CT angiogram (CTA)
  o MRI
  o Other
• Complications
  o fatal bleed
  o ≥2g/dL drop in hemoglobin
  o reoperation for hematoma evacuation
  o other clinical significant bleeding
  o infectious complication
  o VTE
  o PE
• Concomitant meds
  o LMWH
  o Aspirin
  o Plavix
  o platelet inhibitors
  o NSAIDs			

Assessment	Baseline	Baseline – 3 months	3 month
○ Anticoagulation medications outside treatment assignment			
CRF06: VTE Prophylaxis (Inpatient)	X		
• Pre & Post Randomization Prophylaxis Use • Treatment Arm: Aspirin Dosage (Dose, Dose Unit, Route, Date/Time of Start/Stop of Administration) • Treatment Arm: LMWH Dosage (Dose, Dose Unit, Route, Date/Time of Start/Stop of Administration) • Reasons prophylaxis held or discontinued (if applicable) • Doses ordered vs doses received or missed & reason missed • Treatment crossover information: number of doses & therapeutic anticoagulation therapy status (date, dose, reason)			
CRF07: Clinical Follow-up			X
• Documented prescribed prophylaxis and duration • Out of pocket costs • Satisfaction • Prescribed medications • Any other treatment for PE/VTE event • Re-hospitalizations related to PE/VTE event– review medical records • Imaging studies • Post discharge surgeries ○ Planned elective surgeries • Complications (type, severity, treatment) ○ Fatal bleed ○ GI bleed ○ ≥2g/dL drop in hemoglobin ○ reoperation for hematoma evacuation ○ other clinical significant bleeding ○ infectious complication ○ VTE ○ DVT (blood clot in arms/legs) ○ Pulmonary Embolism ○ Imaging studies for bleeding or VTE			

Assessment	Baseline	Baseline – 3 months	3 month
○ Surgical wound infection ○ Surgical wound hematoma ○ Abnormal postoperative bleeding ○ Any complications secondary to treatment since hospitalization			
CRF08: Patient Follow-up			X
• Hospitalizations r/t PE/VTE outside the study center • TSQM: Treatment Satisfaction Questionnaire for Medication			
CRF09: Diagnosis of Infection	X	X	X
• CDC Criteria • Culture Data • Lab Data • Imaging Studies • Wound Characteristics • Time to Wound Closure • Type of Soft Tissue Coverage • Limb Complications (type, severity, treatment)			
CRF10: SAE	X	X	X
Unanticipated events possible related to exposure to study medications (angioedema, agranulocytosis, hepatic injury, Stevens Johnson syndrome), other events that are serious and either related or possibly related to the study, other events that are unexpected and serous and either related or possibly related to the study beyond the expected complications.			

Summary of Protocol Amendments
The following summarizes the major actions taken regarding the master protocol.

Date	Action
3/1/2017	Johns Hopkins Bloomberg School of Public Health IRB (JHBSPH) granted initial approval.
4/11/2017	Initial protocol distributed to sites for submission.
5/26/2017	Amendment for V2 of the protocol approved by JHBSPH IRB. Amendment adds procedures for monitoring adherence and updates consent and recruitment materials.
7/27/2017	V2 of the protocol distributed to sites for submission.
8/16/2017	Amendment for V3 of the protocol approved by JHBSPH IRB. Amendment corrects an omission error in the exclusion criteria when updates were made from V1 to V2 of the protocol.
8/18/2017	V3 of the protocol distributed to sites for submission.
10/18/2017	Administrative amendment updating brochure language approved by JHBSPH IRB.
11/27/2017	Updated brochure distributed to sites for submission.
1/3/2018	Amendment updating text of patient satisfaction questionnaire approved by JHBSPH IRB.
1/12/2018	Updated questionnaire distributed to sites for submission.
9/27/2018	Amendment updating recruitment material to add a weekly adherence survey postcard approved by JHBSPH IRB.
11/6/2018	Amendment making changes to the weekly adherence follow-up instrument questions and change of medical monitor approved by JHBSPH IRB.
12/17/2018	Amendment updating patient follow up questionnaire approved by JHBSPH IRB. Weekly adherence postcard, updated patient follow up questionnaire and change in medical monitor distributed to sites for submission.
6/19/2019	Amendment to modify follow-up procedures to allow for abstraction of medical records for participants who do not return for a research visit approved by JHBSPH IRB.
6/26/2020	Amendment to update protocol with add the capability of screening and enrollment to be conducted remotely by research coordinators in collaboration with on-site advanced practice providers in response to the COVID-19 pandemic.
8/14/2020	Amendment to update protocol to obtain COVID-19 status of all patients enrolled since March 2020 and moving forward.
9/25/2020	Amendment to update protocol to exclude patients with COVID-19 and collect COVID-19 status on all patients enrolled since January 2020. Expanded lost to follow up search options using Limited Access Death Master File (LADMF) of protocol and consent form.
1/22/2021	Amendment to update protocol to change the primary outcome to all-cause mortality, update non-inferiority margin to 0.70%, remove specific aims 3 & 4, remove 1 month window-based follow up, add data collection of ICD-9 codes.
6/1/2021	Amendment to add postcard, text message, and calls for additional follow up.
8/6/2021	Amendment to update total recruitment to 12,400 patients, add phone call/text centralized follow up by coordinating center for lost to follow up patients, remove 6-month limit on medical record review on lost to follow up patients, add use of LexisNexis Accurint System for lost to follow up patients, add follow up post card. Approved by JHSPH IRB.

PREVENT CLOT:
Statistical Analysis Plan for Main Outcome Paper

January 21, 2021

The statistical analysis plan was finalized prior to database lock. Prior to database lock, the only analyses that were performed were (1) those masked to treatment group for purposes of DSMB reporting, (2) a formal DSMB interim analyses of the primary outcome after approximately 4,000 and 8,000 patients completed follow-up.

Per DSMB approval, the study team had access to the following information (masked to treatment arm, site-stratified) during the course of the trial:

- Crossovers: in-patient, at discharge and overall
- Equipoise: discharge without prophylaxis, DVT imaging and PE imaging

1 Randomization, Treatment Initiation, Time Zero

Prophylaxis medication is typically administered in 12 hour increments. Patients may receive up to two doses of prophylaxis prior to enrollment/randomization into the study. After randomization, their next dose of prophylaxis is to be according to their randomized treatment. There will typically be a lag between randomization and initiation of randomized treatment. Lags can occur for a multitude of reasons, as depicted by these examples:

1. Patient is enrolled/randomized at 8 am after 7 am medication. Next dose is 7pm. Lag is 11 hours.
2. Patient is enrolled/randomized at 8 am after 7 am medication, but she is sent to the operating room at 6 pm and all medications are held. Next dose is 7 am next day. Lag is 24 hours.

3. Patient is planned for prophylaxis, but due to another injury and risk of bleeding (e.g., head injury), they will be delayed by several days. Patient enrolled/randomized but medication is not started until cleared for prophylaxis 3 days later. Lag is 96 hours.

There could possibly be differences between medication initiation between treatment arms, particularly in a small subgroup of patients. To address this issue, we will set time zero to be time of randomization.

2 CONSORT Diagram

The CONSORT Diagram will report the following items in sequential order:

1. the number screened patients
2. number of eligible patients
3. the number of patients not enrolled and associated reasons
4. the number of enrolled and randomized patients
5. number randomized to aspirin group, number randomized to low-molecular-weight heparin (LMWH) group
6. within treatment group, the number of late ineligibles, late refusals, and inappropriate enrollments
7. within treatment group, the number initiating treatment protocol
8. within treatment group, information on 90 day follow-up (including separate metrics for key endpoints)
9. within treatment group, the number included in the per-protocol analysis

The independent adjudication committee will make the final determination on late ineligibles and inappropriate enrollments while masked to the treatment arm. Late ineligibles and inappropriate enrollments will be removed from all analyses. The outcomes, complications, adverse events of late ineligibles and inappropriate enrollments who received treatment will be reported, to the extent possible.

3 Follow-up Time

Patients were expected to return for a study follow-up visit at 90 days post admission. If participants are unable to return to the clinic, they may be contacted to complete the 90 days follow up visit via phone or email. In addition, medical record reviews will be conducted to determine whether there was documented clinical/research contact beyond the last study follow-up visit. If that visit occurred less than 90 days following randomization, the end of follow up will be defined as the last study follow-up visit or the last clinical/research contact if applicable, and follow-up time will be the duration between randomization and the end of follow up. A figure showing the distribution of follow-up time through 90 days by treatment group will be produced. Differences between treatment groups based on follow-up time through 90 days will be evaluated. Details of reasons for premature study discontinuation will be presented.

4 Baseline Characteristics

A table will report summary statistics of baseline characteristics of participants by treatment groups. Characteristics will include age, sex, body mass index, tobacco use, history of venous thromboembolism, co-morbidities, additional medications, health insurance status, injury severity score, and injury region.

5 Adherence to Treatment Protocol

As a pragmatic trial, it is up to the treating surgeon to determine the duration of medication of the assigned treatment based on the risk profile of the patient. As such, duration of medication will vary from person to person. To be classified as adherent to treatment, the patient must meet the following criteria:

1. If the patient is prescribed thromboprophylaxis at discharge, the patient must be discharged on the allocated study medication.

2. The patient must have been adherent for at least 80% of their in-hospital study medication doses.

Dosage changes due to non-medical reasons, protocol crossovers due to non-medical reasons, and patient refusal to continue medication will be consid-

ered non-adherence. Summary statistics related to in-hospital and discharge protocol non-adherence will be presented by treatment arm.

6 Serious Adverse Events

By definition, serious adverse events (SAEs) are severe, undesirable, unexpected events that are potentially related to study participation. All SAEs are reported to the Medical Monitor, who makes a determination of relatedness and required action (e.g., stopping medication, informing other sites). A table will report SAEs and relatedness, stratified by treatment group.

7 Outcome Analyses

7.1 Ascertainment

The primary way in which clinical outcome events are ascertained is through standard of care clinical interactions, medical record review, review of the Limited Access Death Master File records, other available death registries, and, in some cases, phone calls.

7.2 Adjudication

For our secondary outcome of cause-specific death, all deaths will be adjudicated into one of the following five categories in terms of certainty of a pulmonary embolism (PE): (a) Certainly PE, (b) More likely PE than something else, (c) Equally likely to be PE than something else, (d) More likely something else than PE and (e) Definitely not PE. For patients in categories (d) or (e), adjudicators will indicate the most likely cause of death.

7.3 Estimands

Throughout this section, death is considered as an event that preempts the observation of any future events. In contrast, we consider those individuals lost-to-followup as being at-risk for future events.

7.3.1 Intention to Treat Analysis

Our primary analysis will use an intention to treat approach. The primary estimand (1) will be estimated using treatment-specific Kaplan-Meier estimators. The other intention-to-treat estimands will be estimated using

treatment-specific cumulative incidence function estimators.The study has more than 90% power to address Estimand (1).

7.3.2 Primary Estimand

All-Cause Mortality

1. Difference (aspirin minus LMWH) in the probability of dying due to any cause by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup.

7.3.3 Secondary Efficacy Estimands

Cause-Specific Mortality

2. Difference (aspirin minus LMWH) in the probability of being *observed* to die due to PE (using categories a and b from Section 7.2) by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup;

3. Difference (aspirin minus LMWH) in the probability of being *observed* to die due to PE (using categories a, b and c from Section 7.2) by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup;

4. Difference (aspirin minus LMWH) in the probability of being *observed* to die due to non-PE (must be in category d or e from Section 7.2) causes of death (e.g., myocardial infarction, stroke, bleeding) by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup;

Non-Fatal Pulmonary Embolism

5. Difference (aspirin minus LMWH) in the probability of being *observed* to have a non-fatal PE by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup, where non-fatal PE will be categorized in (i) aggregated, (ii) sub-classified as massive, sub-massive, clinically significant, clinically non-significant and (iii) sub-classified as segmental, non-segmental;

Deep Vein Thrombosis

6. Difference (aspirin minus LMWH) in the probability of being *observed* to have a DVT by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup; where DVT will be categorized as (i) any, (ii) proximal, and (iii) distal.

7.3.4 Secondary Safety Estimands

Major Bleeding Event

7. Difference (aspirin minus LMWH) in the probability of being *observed* to have a bleeding event by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup;

Wound Complication

8. Difference (aspirin minus LMWH) in the probability of being *observed* to have a wound complication by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup.

Deep Surgical Site Infection

9. Difference (aspirin minus LMWH) in the probability of being *observed* to have a deep surgical site infection by 90 days for eligible patients under assigned treatment, in a world without loss-to-followup;

7.3.5 Per Protocol Analysis

To understand treatment differences in the presence of non-adherence, we will perform a secondary per protocol analysis for the nine estimands. The per protocol estimands will only include the subset of patients classified as protocol adherent, as defined in Section 5. To the extent possible, we will adjust for a limited set of key baseline covariates. Missing baseline covariates will be imputed using multiple imputation.

7.4 Analytic Strategy

- We will test Estimand 1 for non-inferiority using the upper bound of a two-sided 96.2% confidence interval compared to the pre-specified non-inferiority margin of 0.75%.
- If non-inferiority is established at our pre-specified non-inferiority margin, we will test for superiority.
- Two-sided 95% confidence intervals will also be presented for Estimands 2-9 but null-hypothesis significance tests will not be performed.

7.5 Subgroup Analyses

We will perform one subgroup analysis to assess the variation in treatment effect for our primary outcome based on patient age:

1. Age > 60 vs. Age ≤ 60

Interaction tests will be performed to assess heterogeneity of treatment effects.

7.6 Comments

- Due to low event rates, it may be impossible to compute reliable confidence intervals.
- We recognize that precision can be increased by leveraging baseline covariates. To the extent possible, we will leverage age, injury severity, and other key characteristics.

8 Change in Primary Outcome

The primary study outcome was changed from PE-related death to all-cause mortality during the course of the trial.

At the recommendation of an external peer reviewer for the protocol manuscript, the trial's steering committee determined that it was infeasible to adjudicate death due to pulmonary embolism (PE) with reasonable certainty. Misclassification of the primary outcome of PE-related death would bias the results to non-inferiority. As such, the trial's steering committee decided to change the primary outcome from PE-related death to all-cause mortality. All-cause mortality was viewed as more important than PE-related death by our patient stakeholder and protocol committees and had greater scientific reliability. The change in the primary outcome increased the anticipated base rate from 0.25% to 1.00% leading to an increase in the non-inferiority margin from 0.36% to 0.75% to maintain the target sample size of 12,200 and over 90% power. The DSMB was not involved in these decisions due to their masked knowledge of treatment effect from interim analyses. The decision of the trial's steering committee to change the primary outcome and non-inferiority margin was supported by the protocol committee, patient stakeholder committee, and sponsor.

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