BMJ Open

PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): a randomised pragmatic trial protocol comparing aspirin versus low-molecular-weight heparin for blood clot prevention in orthopaedic trauma patients

Robert V O'Toole ,[1] Deborah M Stein,[2] Katherine P Frey,[3] Nathan N O'Hara ,[1] Daniel O Scharfstein,[4] Gerard P Slobogean,[1] Tara J Taylor,[3] Bryce E Haac,[5] Anthony R Carlini,[3] Theodore T Manson,[1] Kuladeep Sudini,[3] C Daniel Mullins,[6] Stephen T Wegener,[7] Reza Firoozabadi,[8] Elliott R Haut,[9] Michael J Bosse,[10] Rachel B Seymour,[10] Martha B Holden,[11] Ida Leah Gitajn,[12] Samuel Z Goldhaber,[13] Alexander L Eastman,[14] Gregory J Jurkovich,[15] Heather A Vallier,[16] Joshua L Gary,[17] Conor P Kleweno,[8] Joseph Cuschieri,[18] Debra Marvel,[19] Renan C Castillo,[3] METRC

To cite: O'Toole RV, Stein DM, Frey KP, *et al*. PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): a randomised pragmatic trial protocol comparing aspirin versus low-molecular-weight heparin for blood clot prevention in orthopaedic trauma patients. *BMJ Open* 2021;**11**:e041845. doi:10.1136/bmjopen-2020-041845

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-041845).

Received 18 June 2020
Revised 27 January 2021
Accepted 25 February 2021

For numbered affiliations see end of article.

Correspondence to
Dr Robert V O'Toole; ROtoole@som.umaryland.edu

ABSTRACT

Introduction Patients who sustain orthopaedic trauma are at an increased risk of venous thromboembolism (VTE), including fatal pulmonary embolism (PE). Current guidelines recommend low-molecular-weight heparin (LMWH) for VTE prophylaxis in orthopaedic trauma patients. However, emerging literature in total joint arthroplasty patients suggests the potential clinical benefits of VTE prophylaxis with aspirin. The primary aim of this trial is to compare aspirin with LMWH as a thromboprophylaxis in fracture patients.

Methods and analysis PREVENT CLOT is a multicentre, randomised, pragmatic trial that aims to enrol 12 200 adult patients admitted to 1 of 21 participating centres with an operative extremity fracture, or any pelvis or acetabular fracture. The primary outcome is all-cause mortality. We will evaluate non-inferiority by testing whether the intention-to-treat difference in the probability of dying within 90 days of randomisation between aspirin and LMWH is less than our non-inferiority margin of 0.75%. Secondary efficacy outcomes include cause-specific mortality, non-fatal PE and deep vein thrombosis. Safety outcomes include bleeding complications, wound complications and deep surgical site infections.

Ethics and dissemination The PREVENT CLOT trial has been approved by the ethics board at the coordinating centre (Johns Hopkins Bloomberg School of Public Health) and all participating sites. Recruitment began in April 2017 and will continue through 2021. As both study medications are currently in clinical use for VTE prophylaxis for orthopaedic trauma patients, the findings of this trial can be easily adopted into clinical practice. The results of this large, patient-centred pragmatic trial will help guide treatment choices to prevent VTE in fracture patients.

Strengths and limitations of this study

- Current guidelines indicate that many fracture patients should receive medication to reduce the risk of venous thromboembolism; however, there is no consensus on the best thromboprophylaxis for this patient population.
- PREVENT CLOT was designed using patient preference research and prescribing trends in orthopaedic trauma to ensure the findings can be easily adopted into clinical practice.
- The study's 12 200 patients will be enrolled at over 20 sites in the USA and Canada and will use broad eligibility criteria to maximise generalisability.
- Patients and providers are not blinded to the treatment allocation; however, we will monitor and report medication adherence by treatment arm.

Trial registration number NCT02984384.

INTRODUCTION

Traumatic injury and the risk of venous thromboembolism

Patients who sustain trauma are well known to be at an increased risk for venous thromboembolism (VTE), including fatal pulmonary embolism (PE).[1] Globally, over 130 million people sustain a fracture each year.[2] Hip fractures are among the most common fracture types and are associated with a high risk of VTE.[3 4] Current guidelines indicate that many fracture patients should receive medication to

reduce the risk of VTE.[5–8] Despite the frequency of these injuries and the potentially devastating impact that VTE can have on patients' lives, the best prophylactic regimen for this patient population remains unknown.

Knowledge gap on VTE prevention

A recent study by the Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlighted a knowledge gap surrounding the prevention of VTE in fracture patients. It concluded that there is 'wide variability in practice patterns, poor scientific support for various therapeutic regimens', and guidelines are needed to 'improve patient care'.[9] While healthcare practitioners clearly need guidelines on VTE prevention in fracture patients,[9] no large, high-quality trials on which to base these guidelines exist.[1] Most current VTE prevention guidelines for orthopaedic trauma patients are based on extrapolated data from arthroplasty patients or elderly patients with isolated hip fractures.[10] Both groups have limited generalisability to the broader orthopaedic trauma population, so VTE prophylaxis decisions for those patients currently lack adequate evidence.

Current VTE prophylaxis practice guidelines for trauma patients

The Eastern Association for the Surgery of Trauma (EAST) and the American College of Chest Physicians (ACCP) currently recommend low-molecular-weight heparin (LMWH) for VTE prophylaxis in general trauma patients.[5 6] As such, many Level-1 trauma centres in the USA and elsewhere routinely use LMWH for fracture patients if they are not contraindicated for chemoprophylaxis.

Evidence from total joint arthroplasty

Aspirin is an inexpensive and widely available generic antiplatelet drug. An emerging body of evidence in total joint arthroplasty patients suggests that aspirin is as effective as other commonly prescribed pharmacological agents in preventing VTE.[11–20] The results of these studies have led the European Society of Anaesthesiologists to recommend aspirin for VTE prophylaxis in arthroplasty and hip fracture patients.[7] While comparable literature in fracture patients is lacking, the growing arthroplasty evidence, combined with the decreased patient burden and limited complication profile associated with aspirin, has led some surgeons to begin prescribing aspirin for VTE prophylaxis in fracture patients.[9]

We acknowledge an emerging body of evidence that suggests direct oral anticoagulants may be comparable to aspirin in preventing VTE in arthroplasty patients.[21 22] However, there remain concerns regarding an increased risk of bleeding for direct oral anticoagulants compared with aspirin.[23 24] Direct oral anticoagulants are also more costly than aspirin, making them less favourable from a patient perspective.[25]

Study objectives

The primary aim of PREVENT CLOT is to compare aspirin to LMWH for thromboprophylaxis in orthopaedic trauma patients. We hypothesise that aspirin is non-inferior to LMWH in preventing all-cause mortality within 90 days of randomisation. The secondary objective is to compare the effects of aspirin versus LMWH in preventing cause-specific mortality, non-fatal PE, deep vein thrombosis (DVT), bleeding complications, wound complications and deep surgical site infections (SSIs) within 90 days of randomisation.

METHODS AND ANALYSIS

Trial design and setting

PREVENT CLOT is a multicentre, randomised, pragmatic trial to compare LMWH versus aspirin for thromboprophylaxis in fracture patients. The study will enrol patients at trauma centres in the USA and Canada and is co-led by the Department of Orthopaedics at the University of Maryland School of Medicine and the Major Extremity Trauma and Rehabilitation Consortium (METRC) Coordinating Center (MCC) at the Johns Hopkins Bloomberg School of Public Health (JHSPH). The recruiting sites are listed in table 1.

Patient and public involvement

The PREVENTion of Clot in Orthopaedic Trauma study (PREVENT CLOT) was designed based on the clinical knowledge gap and input from patients who identified the prevention of VTE and death as high priorities for their care. PREVENT CLOT investigators adhered to the 10-step process for continuous patient engagement in the design and conduct of the trial, and have benefited from the valuable input from a formal Patient Stakeholder Advisory Committee (PSAC).[26] The PSAC includes orthopaedic trauma patients, caregivers, clinicians and representatives from patient advocacy organisations and health insurance providers. The committee meets quarterly to provide feedback on the study design, analysis and interpretation of the findings. In addition to the PSAC involvement, the study team conducted a discrete choice experiment with 232 orthopaedic trauma patients to determine the relative importance of possible study outcomes.[25] The results of this study established our hierarchy of endpoints and non-inferiority margins based on the observed acceptable trade-offs.

Investigational drug status

Both study treatments are Food and Drug Administration (FDA)-approved medications commonly used for the indication proposed in this trial. However, aspirin is considered off-label for the indication of VTE prophylaxis, and an application for an Investigational New Drug (IND) exemption was approved by the FDA for the proposed indications outlined in this protocol. For patients enrolled at Canadian sites, the inpatient administration of aspirin and the aspirin prescribed to study participants at discharge is dispensed by the treating hospital's pharmacy and complies with labelling requirements outlined in the Food and Drug Regulations (C.05.011).

Table 1 Recruiting sites for PREVENT CLOT

Hospital	City, State
Allegheny General Hospital	Pittsburgh, Pennsylvania
Atrium Health – Carolinas Medical Center	Charlotte, New Carolina
Brooke Army Medical Center	San Antonio, Texas
Dartmouth-Hitchcock Medical Center	Lebanon, New Hampshire
Harborview Medical Center	Seattle, Washington
Indiana University – Methodist Hospital	Indianapolis, Indiana
Inova Fairfax Hospital	Falls Church, Virginia
Massachusetts General Hospital	Boston, Massachusetts
McGovern Medical School at UTHealth Houston	Houston, Texas
McMaster University – Hamilton General Hospital	Hamilton, Ontario
MetroHealth Medical Center	Cleveland, Ohio
Rhode Island Hospital – Brown University	Providence, Rhode Island
University of Arizona	Tucson, Arizona
University of Calgary Foothills Medical Centre	Calgary, Alberta
University of Maryland – R Adams Cowley Shock Trauma Center	Baltimore, Maryland
University of Miami – Ryder Trauma Center	Miami, Florida
University of Mississippi Medical Center	Jackson, Mississippi
University of Tennessee – Regional One Medical Center	Memphis, Tennessee
University of Wisconsin Health University Hospital	Madison, Wisconsin
Vanderbilt Medical Center	Nashville, Tennessee
Wake Forest University Baptist Medical Center	Winston-Salem, North Carolina

PREVENT CLOT, PREVENTion of Clot in Orthopaedic Trauma study.

Patient selection

Patients meeting the following eligibility criteria are recruited into PREVENT CLOT:

1. Must be 18 years of age or older.
2. Have a planned operative or non-operative pelvis or acetabular fracture, or any operative extremity fracture proximal to the metatarsals or carpals.
3. Will receive a VTE prophylactic regimen per standard of care at the treating centre.

Patients are excluded if they:

1. Present to the hospital more than 48 hours after injury.
2. Receive more than 2 doses of LMWH or aspirin for initial VTE prophylaxis prior to consent.
3. Are on long-term anticoagulants.
4. Have been diagnosed with a VTE within the last 6 months.
5. Are on therapeutic, as opposed to prophylactic, anticoagulants at the time of admission.
6. Are diagnosed with an indication for therapeutic anticoagulants that will require therapeutic anticoagulation.
7. Have an allergy to aspirin or non-steroidal anti-inflammatory drugs, or a history of heparin-induced thrombocytopenia, or other medical contraindication to anticoagulants.
8. Take daily aspirin with a dose greater than 81 mg for medical reasons.
9. Have an underlying chronic clotting disorder that requires full dose anticoagulation or is a contraindication to VTE chemoprophylaxis.
10. Have end-stage renal disease or impaired creatinine clearance of less than 30 mL/min at the time of screening.
11. Are pregnant or lactating.
12. Speak neither English nor Spanish.
13. Are incarcerated.
14. Are likely to have severe problems maintaining follow-up.
15. A diagnosis of COVID-19 at the time of fracture fixation or in the 3 months prior to fixation.

All patients screened for eligibility are documented as (1) eligible and included, (2) eligible and missed, and (3) excluded. In addition, all reasons that eligible patients refuse participation in the trial are documented.

Patient recruitment and screening

Once eligibility is confirmed, the research coordinator or a clinician certified to participate in this study completes the informed consent process with the eligible study patient or a legally authorised representative (LAR). Given the distressed condition of many eligible patients on admission to a participating trauma centre, and the difficulty in enrolling patients immediately on presentation to a trauma centre, the protocol allows for patients to receive up to 2 doses of the centre's standard of care VTE prophylaxis regimen prior to consent and randomisation. If a patient is unable to consent before the third dose of anticoagulation therapy is administered, and a LAR is not available, the patient is not eligible for study participation. 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 enrolment. Patients who are enrolled but later determined to have met an exclusionary condition that was present at the time of enrolment will be reviewed by the adjudication committee masked to treatment arm. If the adjudication committee determines the patient should be classified as a late ineligible patient, they will be removed from the study, as recommended by Fergusson *et al*.[27] If these participants receive study drugs, they are followed for any adverse events, but their results are not included in the study.

Study interventions

Low-molecular-weight heparin (LMWH)

Enrolled patients are prescribed a 30 mg dose of LMWH administered subcutaneously, two times per day. Adjusted dosing is permitted for obese patients and patients with renal disease, based on each study site's existing protocols.

Aspirin

Aspirin is prescribed at an 81 mg dose, two times per day. The 81 mg dose has demonstrated effectiveness in reducing the risk of clots in the total joint arthroplasty literature.[19] The two times per day frequency was selected for consistency between the two treatment arms and provides an equivalent daily dose with the Pulmonary Embolism Prevention trial.[10]

Randomisation

Patients are randomised with a 1:1 ratio with variable block sizes and stratified by clinical site using an automated structure embedded into the Research Electronic Data Capture (REDCap) system.[28] Research coordinators initiate randomisation at each clinical site. Neither the patient nor the treating physician is blinded to the treatment allocation. Treatment allocation is concealed during data monitoring and analysis.

Duration and indication for VTE prophylaxis

No consensus exists regarding the recommended duration nor exact indication for VTE prophylaxis following a fracture, and VTE protocols currently vary between sites. Existing guidelines also vary in their recommendations, depending on the type and severity of the injury. To reflect real-world practice, the duration and indications for VTE prophylaxis are determined by the VTE prophylaxis guidelines at each centre. However, the study requires all VTE doses for enrolled inpatients to be recorded in the study data. These data are monitored weekly by the MCC to ensure the duration of prophylaxis is non-differential between treatment arms at each centre. Sites are notified if differential prescribing between treatment arms is observed.

Outcome ascertainment and adjudication

Primary outcome

The primary outcome is all-cause mortality within 90 days of randomisation. Data regarding patient death are collected from the medical record, including the treating physician's determination of death and autopsy report, when available, as well as any available sources such as the Limited Access Death Master File, other death registries, and, in some cases, phone calls.

The primary 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 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 Data and Safety Monitoring Board (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.

Secondary efficacy outcomes

Secondary efficacy outcomes include cause-specific death, non-fatal PE and DVT.

Cause-specific death will be adjudicated with a specific focus on PE-related death. The study's three-person adjudication committee is composed of experts not otherwise involved in any other aspect of the study. The committee is blinded to the treatment arm and receives data with the goal of classifying the death into one of five categories: (1) *Certainly PE* (eg, an autopsy indicates cause of death), (2) *More likely to be caused by PE than something else* (eg, clinical information available indicating likely cause of death, but no autopsy or corroborating data available), (3) *Equally likely to be caused by PE or something else* (eg, 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), (4) *More likely to be a cause other than PE* (eg, the clinical course was highly suggestive that the cause of death was not PE), and (5) *Certainly not due to PE* (eg, the cause of death was not related to a PE). There must be agreement among at least two of the three committee members, with no more than one level of disagreement among members, for the cause of death category determination to be finalised.

Non-fatal PE is another secondary efficacy outcome. The local site investigators categorise PE events, which are adjudicated centrally by the adjudication committee as one of four levels: *Massive* and *submassive* PE events are defined based on the American Heart Association recommendations[29]; *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 subclassified as being segmental or non-segmental. Similar to the adjudication of the cause of death, the categorisation of PE requires two-thirds consensus from the adjudication committee.

The final secondary efficacy outcome is DVT. To be included as a DVT outcome, the event must be symptomatic and confirmed with imaging. We will report all confirmed symptomatic DVT events, and report events subclassified by proximal DVT and distal DVT.

Secondary safety outcomes

Safety outcomes include bleeding complications, wound complications and deep SSI. These outcomes are not adjudicated by the adjudication committee. 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 haemoglobin level of 20 g/L 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.[30] Wound complications include wound drainage, haematoma or seroma of an orthopaedic injury that requires a subsequent surgery. Deep SSI 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.[31] The fracture-related infection definition, an alternative to the aforementioned criteria,[32] was published after initiation of this study and, thus, is not considered when defining deep SSI.

Follow-up

Participants are to be assessed at their first regularly scheduled clinical appointment that occurs 90 days after randomisation. If the patient does not return to the clinic after 90 days post-randomisation, they are contacted to complete the follow-up assessment by a phone call or email. The 90-day assessment is performed by a research staff member at the participating centre and will evaluate the occurrence of any clinical outcomes, including VTE events or complications secondary to treatment since their hospitalisation. For each event identified, the participant completes a release of information form that will allow the research staff to obtain records related to the event if it occurred outside the index facility. Additionally, medical records are carefully reviewed to assess for any complications treated at the index facility, including in the clinic, emergency department or during a rehospitalisation.

If a participant cannot be contacted and does not return for a final research visit, medical records are abstracted through the last clinical encounter occurring up to 6 months following injury. If no visit occurs in this interval, then the last visit is reported as the end of follow-up for that participant. At the end of the study, any participant with less than 90 days of follow-up post-randomisation will be searched using other available sources, such as the Limited Access Death Master File, to capture any loss to follow-up that occurred as a result of death.

Attempts will be made to obtain medical records or autopsy reports for all participants who are discovered to be deceased. If the participant dies at home, family members are asked to provide a cause of death, if known. If a patient's death is identified through a publicly available source, attempts are made to follow-up with family for information on the cause of death.

Maximising patient retention

Every effort will be made to retain participants in the study. The study participants will receive a $20 honorarium in recognition of their involvement in the study after completing their 90-day post-randomisation assessment.

Medication adherence

Accurate information on inpatient medication adherence and the medication prescribed at discharge is important to the internal validity of the trial and will be closely monitored; research staff at each site complete a daily adherence report while a participant is an inpatient and at time of discharge. To be classified as protocol adherent, patients must meet 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. Medically necessary changes to the VTE prophylaxis are not considered non-adherence to the protocol. As the study is designed to investigate the effect of a hospital protocol for VTE prophylaxis, the study measures adherence during the hospitalisation and at discharge. Adherence after discharge from the hospital is not accounted for in this study.

Data management and monitoring

A certification process is used as the basis for training and certification of the study personnel involved in data collection. Ongoing data edits and audits are performed to ensure the collection of high-quality data. The continuous and timely flow of data from the centres to the MCC is an essential requirement for maintaining data quality.

Weekly enrolment reports are distributed to each centre summarising recruitment, data completion and timeliness of data entry. Data queries using the trial's REDCap database are disseminated and expected to be resolved on a monthly basis.[28] Site visits are conducted to monitor data and ensure quality data capture at least once, and more frequently depending on enrolment volume.

To prevent threats to the internal validity of the study, trial leadership obtained approval from the DSMB prior to the study began enrolment to have real-time oversight of site-level data that is masked to the treatment allocation. The data monitoring includes the frequency of missed inpatient doses, inpatient and discharge treatment crossover rates with reasons, VTE testing rates and study follow-up rates.

Data and Safety Monitoring Board

An independent DSMB is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety, evaluate recruitment and assess overall data quality. The DSMB is a multidisciplinary group that will meet twice a year to review data or other

issues. The DSMB may request more frequent meetings if needed. It may also request additional safety reports on a more frequent basis. The Medical Monitor prospectively reviews monthly mortality data by masked treatment arm, as well as all serious adverse events, and has the option to request a teleconference with the study's investigators based on the result of these reviews.

Estimands

Following the Addendum to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guidance,[33] we define a series of estimands that are the target of estimation in this trial (table 2). All estimands focus on events that occur within 90 days of randomisation. We will treat all-cause death as a competing risk for non-fatal events and cause-specific death as a competing risk for other causes of death. The primary analysis will use an intention-to-treat approach, as the pragmatic design aims to determine non-inferiority at the policy level. A secondary analysis will estimate the effect among those adherent to the treatment protocol.

Non-inferiority margins

The primary hypothesis is that aspirin will be non-inferior to LMWH with respect to all-cause mortality. The trial's non-inferiority margin was derived from patient preference research and a survey of clinical experts that indicated a willingness to accept a 0.75% absolute increase in the risk of death in exchange for a specific set of benefits related to aspirin over LMWH.[25] These benefits include preferences for oral medication over injectable medicine, less risk of bruising and lower out of pockets costs.

Statistical methods

Inference for the primary estimand (E1) will be calculated using treatment-specific Kaplan-Meier estimators. Secondary estimands (*E2–E9*) will be based on cumulative incidence function estimation where individuals who are lost to follow-up prior to the endpoint of interest are censored.[34] A secondary analysis will estimate the estimands using a per-protocol analysis. The per-protocol estimands will only include the subset of patients classified as protocol adherent. To the extent possible, we will adjust for baseline differences between the per-protocol treatment groups. Missing baseline covariates will be imputed using multiple imputation.

To evaluate the primary hypothesis regarding all-cause mortality, we will compare the upper bound of a two-sided 96.2% CI for the primary intention-to-treat estimand to the prespecified non-inferiority margin of 0.75%. If non-inferiority is established, we will test the primary estimand for superiority. For all other estimands, we will report point estimates with two-sided 95% CIs. We will not perform hypothesis testing for the secondary estimands.

Subgroup analyses

Based on the credible subgroups criteria,[35] we plan to conduct subgroup analysis to compare the effects of the primary estimand based on patient age. Age will be stratified into two levels: under 60 years of age, and 60 years of age or older. An interaction test will be performed to assess the heterogeneity of the treatment effect. We hypothesise that aspirin will be more effective in preventing death in

Table 2 List of trial estimands with definitions

Estimand	Definition
Primary outcome	
E1	All-cause mortality
	Difference (aspirin minus LMWH) in the probability of dying of any cause
Secondary efficacy outcomes	
	Cause-specific mortality
E2	Difference in the probability of being observed to die due to PE (adjudication categories a and b) under assigned treatment
E3	Difference in the probability of being observed to die due to PE (adjudication categories a, b and c)
E4	Difference in the probability of being observed to die due to non-PE (categories d or e) related causes of death
	Non-fatal pulmonary embolism
E5.1	Difference in the probability of being observed to have a non-fatal PE
E5.2	Difference in the probability of being observed to have a massive non-fatal PE
E5.3	Difference in the probability of being observed to have a submassive non-fatal PE
E5.4	Difference in the probability of being observed to have a clinically significant non-fatal PE
E5.5	Difference in the probability of being observed to have a clinically non-significant non-fatal PE
E5.6	Difference in the probability of being observed to have a segmental non-fatal PE
E5.7	Difference in the probability of being observed to have a non-segmental non-fatal PE
	Deep vein thrombosis
E6.1	Difference in the probability of being observed to have symptomatic deep vein thrombosis
E6.2	Difference in the probability of being observed to have proximal deep vein thrombosis
E6.3	Difference in the probability of being observed to have distal deep vein thrombosis
Secondary safety outcomes	
E7	*Bleeding event*
	Difference in the probability of being observed to have a bleeding event
E8	*Wound complication*
	Difference in the probability of being observed to have a wound complication
E9	*Deep surgical site infection*
	Difference in the probability of being observed to have a deep surgical site infection.

LMWH, low-molecular-weight heparin; PE, pulmonary embolism.

patients 60 years of age or older than in patients under 60 years of age through a different mechanism of myocardial infarction prevention—an event that is much more common in patients 60 years of age or older.[17 36]

Sample size determination

The study is designed to enrol 12 200 patients. Assuming an estimated risk of death in the LMWH arm of 1.0%,[37 38] the proposed sample size provides 95% power to demonstrate the non-inferiority of aspirin with a non-inferiority margin of 0.75% at the upper bound of a two-sided 96.2% CI, as compared with LMWH. These calculations account for two interim analyses and allow for an attrition rate up to 7.5%.

Interim analysis

We have two planned interim analyses to monitor trial safety based on all-cause mortality. The first and second interim analyses were performed when approximately one-third (n=4000) and two-thirds (n=8000) of patients were expected to complete 90 days of follow-up. The primary aim of each interim analysis was to ensure that there is not a differential effect of treatment on death by 90 days after randomisation. To preserve the type I error rate, we will use the alpha-spending approach. This approach statistically dictates stopping early for harm if either at the first interim analysis, a 99.6% CI for the difference in all-cause mortality at 90 days excludes zero, or at the second interim analysis, a 98.8% CI for the difference in all-cause mortality at 90 days excludes zero.

The study's biostatistician presented the masked results of the analysis, including CIs, to the DSMB. Following the review of each interim analysis, the DSMB made a formal recommendation to continue the trial. The study team did not have access to either the results of the analysis or the substance of the DSMB deliberations. After both interim analyses, the DSMB recommended that the trial continues unmodified.

ETHICS AND DISSEMINATION

The study protocol, including the written consent form (an example of the consent form is included as online supplemental file), was approved by the Institutional Review Board (IRB) at JHSPH, the FDA, Health Canada and the local IRB at each participating centre. The trial has been registered with Clinical Trials.gov (NCT02984384). The first patient was enrolled into the trial on 24 April 2017. We anticipate enrolment and follow-up to be completed by the end of 2021.

Orthopaedic trauma patients are known to be at an increased risk of VTE.[1] While most clinical guidelines currently recommend LMWH for VTE prophylaxis in the general trauma population,[5 6] recent total joint arthroplasty literature suggests possible clinical benefits,[7 11–20] in addition to the decreased administration burden of low-dose aspirin for VTE prevention. PREVENT CLOT aims to definitively compare LMWH with aspirin for non-inferiority as a thromboprophylaxis in orthopaedic trauma patients. The successful enrolment of the proposed 12 200 patient sample will make PREVENT CLOT the largest trial in orthopaedic trauma to date.

PREVENT CLOT is specifically designed to be pragmatic and generate clinically relevant findings. As both medications are currently being used for VTE prophylaxis,[9] the findings of this study can be easily adopted into clinical practice. The rigorous and practical design is also responsive to patient preference and prescribing trends in orthopaedics.[25] The study's 12 200 patients will be enrolled at over 20 sites in the USA and Canada and will use broad eligibility criteria to improve generalisability. Regular training of research staff and site monitoring have been implemented to ensure a consistently applied protocol and high data quality. The secondary endpoints of cause-specific death and non-fatal PE will be adjudicated under concealed treatment allocation conditions. The trial is benefiting from the continuous engagement of patients and other stakeholders, as well as over 200 patients that responded to pre-study surveys designed to guide the trial design.[25]

The trial has several limitations. The patients and providers are not blinded to the treatment allocation. Given the differential patient preferences for the routes of administration of the two medications, we are monitoring site-level medication adherence and discharge prescribing to ensure similar rates on a weekly basis. Lacking true equipoise, some providers may differentially screen for study endpoints. However, this practice is also being actively monitored. In addition, medication adherence is accounted for in the per-protocol analysis.

We will disseminate the findings of the trial through presentations at regional, national and international scientific conferences and public forums. The primary results and secondary findings will be submitted for peer-reviewed publication. In addition, we will seek widespread dissemination to the general public in collaboration with our study partners, such as the National Blood Clot Alliance and the American Trauma Society.

The optimal VTE prophylaxis for fracture patients remains controversial. Emerging evidence in arthroplasty research suggests the clinical benefits of aspirin for VTE prevention and is a preferred medication of patients.[11–20 25] PREVENT CLOT has been designed with a patient-centred approach to inform future orthopaedic trauma practice regarding this important decisional dilemma for patients and other stakeholders.

Author affiliations
[1]Department of Orthopaedics, University of Maryland Baltimore, Baltimore, Maryland, USA
[2]Department of Surgery, University of California in San Francisco, San Francisco, California, USA
[3]METRC Coordinating Center, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
[4]Department of Population Health Sciences, University of Utah, Salt Lake City, Utah, USA

[5]Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland, USA
[6]Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA
[7]Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[8]Department of Orthopaedic Surgery and Sports Medicine, University of Washington - Harborview Medical Center, Seattle, Washington, USA
[9]Department of Surgery, Johns Hopkins School of Medicine, Baltimore, Maryland, USA
[10]Department of Orthopaedic Surgery, Atrium Health, Charlotte, North Carolina, USA
[11]Department of Orthopaedic Surgery, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA
[12]Department of Orthopaedics, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA
[13]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA
[14]Department of Surgery, University of Texas Southwestern Medical School, Dallas, Texas, USA
[15]Department of Surgery, University of California Davis, Davis, California, USA
[16]Department of Orthopaedics, MetroHealth System, Cleveland, Ohio, USA
[17]Department of Orthopedic Surgery, University of Texas McGovern Medical School, Houston, Texas, USA
[18]Department of Surgery, University of Washington - Harborview Medical Center, Seattle, Washington, USA
[19]PREVENT CLOT Stakeholder Committee, Baltimore, Maryland, USA

Acknowledgements The authors are grateful to the following individuals for their contributions to this study: Protocol Committee: Mark A. Crowther, MD, MSc (McMaster University, Hamilton General Hospital); Brianna E. Fowler, MS, BS (METRC Coordinating Centre at the Johns Hopkins Bloomberg School of Public Health); Gregory A. Zych, DO (University of Miami Ryder Trauma Centre). Data and Safety Monitoring Board: Marc Swiontkowski, MD (Chair); Gregory A. Brown, MD, PhD; Thomas A. Decoster, MD; Eli Powell, MD; Gregory M. Vercellotti, MD (Medical Monitor); S.D. Walter, PhD; Jeffrey L. Wells. Patient Stakeholder Advisory Committee: Stephen Breazeale, MSN, NP (Yale University); Randolf B. Fenninger, JD (National Blood Clot Alliance; Protocol Committee); Stephen Fisher, MD, PhD (Chesapeake Employers' Insurance Company; Protocol Committee); Eileen Flores, MSW (American Trauma Society); Steven Herndon Jr.; Katherine Joseph, MPH (American Trauma Society); David Wells; Sara Wyen (National Blood Clot Alliance). Other Collaborators (by site at time of study) *Allegheny General Hospital:* Daniel T. Altman, MD; Traci Salopek, LSW; *Atrium Health – Carolinas Medical Centre:* Christine Churchill, MA; Kyle Cunningham, MD, MPH; Susan L. Evans, MD, MBA; Toan T. Huynh, MD; David G. Jacobs, MD; Madhav A. Karunakar, MD; Laurence B. Kempton MD; Stephen H. Sims, MD; *Brooke Army Medical Center:* Eric Martinez, BS; *Dartmouth-Hitchcock Medical Centre:* Peter DePalo Sr., BS, CRC; *Harborview Medical Centre:* Julie Agel, MA; Hikmatullah Arif, BS; *Inova Fairfax Medical Campus:* James S. Ahn, JD, MS, Jaslynn A. N. Cuff, MA; Michael Holzman, MD; A. Stephen Malekzadeh, MD; Farhanaz Panjshiri, MS, Lolita Ramsey, PhD, RN; Jennifer L. Rodriguez, MD; Jeff E. Schulman, MD; Cary C. Schwartzbach, MD; Mario P. Zambito, MD; *Massachusetts General Hospital:* Elizabeth M. Allen, BS; Mira Bansal, BA; Kerry A. Breen, BS; Marilyn Heng, MD, MPH; Michael F. McTague, MPH; *McGovern Medical School at UTHealth Houston:* Garrett B. Jost, MD; Stephen J. Warner, MD, PhD; *McMaster University, Hamilton General Hospital:* Jodi Gallant, MSc, Jordan Leonard, BSc; Paula McKay, BSc; *MetroHealth System:* Mary A. Breslin, BA; *Rhode Island Hospital – Brown University:* Stephanie N. Lueckel, MD, ScM; *University of Arizona:* Jason Lowe, MD; John T. Ruth, MD; Lisa Marie Truchan, MD; Jason R. Wild, MD; *University of Calgary, Foothills Medical Centre*: Aftab Akbari, RN; Richard Buckley, MD, FRC; Paul M. Cantle, MD, MBT; Leah C. Kennedy, RN; Karin Lienhard, PhD; C.Ryan Martin, MD; Stephanie Yee, BSc; *University of Maryland R Adams Cowley Shock Trauma Centre:* Jared J. Atchison, MD; Mitchell W. Baker, BS; Megan Camara, BSN, RN; Daniel W. Connelly, BS; Genaro DeLeon, MS; Haley K. Demyanovich, MPS, BA; Blessing E. Enobun, MD, MPH; Qasim M. Ghulam, MS; Zachary D. Hannan, BS; Andrea L. Howe, BS; Marckenley Isaac, MD, MS; Aaron J. Johnson, MD; Chris Langhammer, MD, PhD; Christopher T. LeBrun, MD; Dimitrius P. Marinos, BS; Phillip C. McKegg, MS; Alexandra Mulliken, BS; Jason W. Nascone, MD; Raymond Pensy, MD; Andrew N. Pollak, MD; Joshua S. Rudnicki, BS; Michael G. Schloss, DO; Marcus F. Sciadini, MD; Ugochukwu N. Udogwu, MD; Syed M. R. Zaidi, MD; *University of Miami Ryder Trauma Centre:* Katherine Napuri, BS; Stephen M. Quinnan, MD; Dinorah Rodriguez, RN, BSN; Gabriela Zych, CCRC, BS; *University of Mississippi Medical Centre:* Heather Champion, LPN; John Morellato, MD; *University of Tennessee Regional One Health:* Michael J. Beebe, MD; *University of Wisconsin*: Deborah Brauer, MS; Christopher M. Domes, MD; Christopher Doro, MD; David C. Goodspeed, MD; Kristina Parvanta Johnson, ATC, MPA; Gerald J. Lang, MD; *Vanderbilt Medical Centre:* Robert H. Boyce, MD; Vamshi Gajari, MD; Charles Pritchett, BS; Elsa B. Rodriguez, MD; Daniel J. Stinner, MD, PhD; Karen M. Trochez, MA; *Wake Forest Baptist Medical Centre:* Sharon Babcock, MD; James B. Goodman, MBA; Holly T. Pilson, MD.

Collaborators Allegheny General Hospital: Gregory T. Altman, MD; Atrium Health – Carolinas Medical Center: A. Britton Christmas, MD; Brooke Army Medical Center: Patrick M. Osborn, MD; Jessica C. Rivera, MD, PhD (Protocol Committee; now at Louisiana State University); Inova Fairfax Medical Campus: Robert A. Hymes, MD; Indiana University Methodist Hospital: Greg E. Gaski, MD (Protocol Committee) (now at Inova Fairfax Hospital), Roman M. Natoli, MD, PhD; Massachusetts General Hospital/Brigham and Women's Hospital: George C. Velmahos, MD, PhD (Protocol Committee, at Massachusetts General Hospital), Michael J. Weaver, MD (at Brigham and Women's Hospital); McGovern Medical School at UTHealth Houston: Bryan A. Cotton, MD, MPH (Protocol Committee); McMaster University, Hamilton General Hospital: Herman Johal, MD, MPH (Protocol Committee); Niv Sne, MD, BSc; Rhode Island Hospital – Brown University: Roman Hayda, MD; Andrew R. Evans, MD; University of Arizona: Christina L. Boulton, MD; Bellal Joseph, MD (Protocol Committee); University of Calgary, Foothills Medical Centre: Prism S. Schneider, MD, PhD (Protocol Committee); University of Maryland R Adams Cowley Shock Trauma Center: Yasmin Degani, MPH; University of Miami Ryder Trauma Center: Rishi Rattan, MD (Protocol Committee); University of Mississippi Medical Center: Patrick F. Bergin, MD; Matthew E. Kutcher, MD, MS; University of Tennessee Regional One Health: Martin A. Croce, MD; John C. Weinlein, MD (Protocol Committee); University of Wisconsin: Paul S. Whiting, MD; Vanderbilt Medical Center: William Obremskey, MD, MPH; Oscar D. Guillamondegui, MD, MPH (Protocol Committee); Wake Forest Baptist Medical Center: Eben A. Carroll, MD; Preston R. Miller, MD.

Contributors RVO, DMS, GPS, TJ, BEH, ARC, TTM, CDM, STW, RF, ERH, DM and RCC each made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, revised the protocol critically for important intellectual content and approved the final version to be published. KPF made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, wrote the first draft of the protocol. NNO made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, wrote the first draft of this manuscript. DOS designed the data analysis and management plan, and revised the protocol critically for important intellectual content and approved the final version to be published. KS, MJB, RBS, MBH, ILG, SZG, AE, GJJ, HAV, JLG, CPK and JC revised the protocol critically for important intellectual content. All authors approved the final version to be published.

Funding This work was funded through a Patient-Centred Outcomes Research Institute (PCORI) Award (PCS-1511–32745).

Disclaimer The sponsor had no role in the trial's design or conduct; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript for submission.

Competing interests CDM has received grant funding as PI from Merck and receives consulting income from AstraZeneca, Bayer Pharmaceuticals, Janssen/J&J, Merck and Pfizer. ERH is/was the primary investigator of contracts from The Patient-Centred Outcomes Research Institute (PCORI) entitled 'Preventing Venous Thromboembolism: Empowering Patients and Enabling Patient-Centred Care via Health Information Technology' (CE-12-11-4489) and 'Preventing Venous Thromboembolism (VTE): Engaging Patients to Reduce Preventable Harm from Missed/Refused Doses of VTE Prophylaxis' (DI-1603-34596); is the primary investigator of a grant from the Agency for Healthcare Research and Quality (AHRQ) (1R01HS024547) entitled 'Individualised Performance Feedback on Venous Thromboembolism Prevention Practice,' and is a co-investigator on a grant from the NIH/NHLBI (R21HL129028) entitled 'Analysis of the Impact of Missed Doses of Venous Thromboembolism Prophylaxis'; receives research grant support from the DOD/Army Medical Research Acquisition Activity and has received grant support from the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF); receives book royalties from Lippincott, Williams, Wilkins; and is a paid consultant to Vizient for their HIIN Venous Thromboembolism (VTE) Prevention Action Network.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Robert V O'Toole http://orcid.org/0000-0003-0537-3474
Nathan N O'Hara http://orcid.org/0000-0003-0537-3474

REFERENCES

1 Barrera LM, Perel P, Ker K. Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev* 2013;28:CD008303.
2 Haagsma JA, Graetz N, Bolliger I, *et al*. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the global burden of disease study 2013. *Inj Prev* 2016;22:3–18.
3 Geerts WH, Code KI, Jay RM, *et al*. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994;331:1601–6.
4 Haut ER, Chang DC, Pierce CA, *et al*. Predictors of posttraumatic deep vein thrombosis (DVT): hospital practice versus patient factors-an analysis of the National trauma data bank (NTDB). *J Trauma* 2009;66:994–1001. discussion 999-1001.
5 Falck-Ytter Y, Francis CW, Johanson NA, *et al*. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. *Chest* 2012;141:e27 8S–325.
6 Rogers FB, Cipolle MD, Velmahos G, *et al*. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. *J Trauma* 2002;53:142–64.
7 Jenny J-Y, Pabinger I, Samama CM, *et al*. European guidelines on perioperative venous thromboembolism prophylaxis: aspirin. *Eur J Anaesthesiol* 2018;35:123–9.
8 National Institute for Health and Care Excellence (UK). *Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism*. London, 2019.
9 Sagi HC, Ahn J, Ciesla D, *et al*. Venous thromboembolism prophylaxis in orthopaedic trauma patients: a survey of OTA member practice patterns and OTA expert panel recommendations. *J Orthop Trauma* 2015;29:e355–62.
10 Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention (PEP) trial. *Lancet* 2000;355:1295–302.
11 Jameson SS, Baker PN, Charman SC, *et al*. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after knee replacement: a non-randomised comparison using national joint registry data. *J Bone Joint Surg Br* 2012;94:914–8.
12 Drescher FS, Sirovich BE, Lee A, *et al*. Aspirin versus anticoagulation for prevention of venous thromboembolism major lower extremity orthopedic surgery: a systematic review and meta-analysis. *J Hosp Med* 2014;9:579–85.
13 Raphael IJ, Tischler EH, Huang R, *et al*. Aspirin: an alternative for pulmonary embolism prophylaxis after arthroplasty? *Clin Orthop Relat Res* 2014;472:482–8.
14 An VVG, Phan K, Levy YD, *et al*. Aspirin as thromboprophylaxis in hip and knee arthroplasty: a systematic review and meta-analysis. *J Arthroplasty* 2016;31:2608–16.
15 Ogonda L, Hill J, Doran E, *et al*. Aspirin for thromboprophylaxis after primary lower limb arthroplasty: early thromboembolic events and 90 day mortality in 11,459 patients. *Bone Joint J* 2016;98-B:341–8.
16 Tan TL, Foltz C, Huang R, *et al*. Potent anticoagulation does not reduce venous thromboembolism in high-risk patients. *J Bone Joint Surg Am* 2019;101:589–99.
17 Rondon AJ, Shohat N, Tan TL, *et al*. The use of aspirin for prophylaxis against venous thromboembolism decreases mortality following primary total joint arthroplasty. *J Bone Joint Surg Am* 2019;101:504–13.
18 Parvizi J, Ceylan HH, Kucukdurmaz F, *et al*. Venous thromboembolism following hip and knee arthroplasty: the role of aspirin. *J Bone Joint Surg Am* 2017;99:961–72.
19 Parvizi J, Huang R, Restrepo C, *et al*. Low-dose aspirin is effective chemoprophylaxis against clinically important venous thromboembolism following total joint arthroplasty: a preliminary analysis. *J Bone Joint Surg Am* 2017;99:91–8.
20 Hood BR, Cowen ME, Zheng HT, *et al*. Association of aspirin with prevention of venous thromboembolism in patients after total knee arthroplasty compared with other anticoagulants: a noninferiority analysis. *JAMA Surg* 2019;154:65–72.
21 Matharu GS, Garriga C, Whitehouse MR, *et al*. Is aspirin as effective as the newer direct oral anticoagulants for venous thromboembolism prophylaxis after total hip and knee arthroplasty? an analysis from the National joint Registry for England, Wales, Northern Ireland, and the Isle of man. *J Arthroplasty* 2020;35:2631–9.
22 Anderson DR, Dunbar M, Murnaghan J, *et al*. Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. *N Engl J Med* 2018;378:699–707.
23 Bala A, Huddleston JI, Goodman SB, *et al*. Venous thromboembolism prophylaxis after TKA: aspirin, warfarin, enoxaparin, or factor Xa inhibitors? *Clin Orthop Relat Res* 2017;475:2205–13.
24 Nielen JTH, Dagnelie PC, Emans PJ, *et al*. Safety and efficacy of new oral anticoagulants and low-molecular-weight heparins compared with aspirin in patients undergoing total knee and hip replacements. *Pharmacoepidemiol Drug Saf* 2016;25:1245–52.
25 Haac BE, O'Hara NN, Mullins CD, *et al*. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. *BMJ Open* 2017;7:e016676.
26 Mullins CD, Abdulhalim AM, Lavallee DC. Continuous patient engagement in comparative effectiveness research. *JAMA* 2012;307:1587–8.
27 Fergusson D, Aaron SD, Guyatt G, *et al*. Post-Randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4.
28 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
29 Jaff MR, McMurtry MS, Archer SL, *et al*. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American heart association. *Circulation* 2011;123:1788–830.
30 Anderson DR, Dunbar MJ, Bohm ER, *et al*. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Intern Med* 2013;158:800–6.
31 National Healthcare Safety Network. Surgical site infection events. centers for disease control and prevention. Available: https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf [Accessed 21 Jun 2019].
32 Metsemakers WJ, Morgenstern M, McNally MA, *et al*. Fracture-related infection: a consensus on definition from an international expert group. *Injury* 2018;49:505–10.
33 European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the Guideline on statistical principles for clinical trials. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf [Accessed 15 Feb 2020].
34 Satagopan JM, Ben-Porat L, Berwick M, *et al*. A note on competing risks in survival data analysis. *Br J Cancer* 2004;91:1229–35.
35 Sun X, Briel M, Walter SD, *et al*. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117.
36 Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, *et al*. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–60.
37 Haac BE, O'Hara NN, Manson TT, *et al*. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: a patient-centered randomized controlled trial. *PLoS One* 2020;15:e0235628.
38 FLOW Investigators, Bhandari M, Jeray KJ, *et al*. A trial of wound irrigation in the initial management of open fracture wounds. *N Engl J Med* 2015;373:2629–41.

ATTACHMENT A: 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 5; 9/25/2020

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. It is up to you whether or not you want to be in this study. If you decide not to join the study, there will be no impact on your medical care. If you decide to join the study, you may quit at any time. Please ask the study doctor or staff to explain any words or procedures that are not clear. Please ask as many questions as you like. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

People who have surgery or trauma are at risk for blood clots. The purpose of this research study is to help figure out the best way to prevent blood clots after trauma. Blood clots can be very serious and can lead to death. Right now, doctors use two different medicines to prevent blood clots, but they don't know which one is better. One of these medicines to prevent blood clots is called low molecular weight heparin, or Lovenox. The other medicine doctors sometimes use is aspirin. This study is being done to find out whether low molecular weight heparin (Lovenox/Enoxaparin) or aspirin is better in preventing life threatening blot clots in trauma patients. Patients who join this study will get either the low molecular weight heparin (Lovenox/Enoxaparin) or aspirin to prevent blood clots. The low molecular weight heparin (Lovenox/Enoxaparin) is given by injection (shot). The aspirin is a pill taken by mouth or given through a feeding tube. Patients in this study will start their medicine in the hospital and then take the same medicine once they go home. We will then compare the medicines to see which one was better at preventing blood clots.

The PREVENT CLOT study protocol is the confidential intellectual property of the PREVENT CLOT Principal Investigators, Steering Committee, and the University of Maryland Baltimore and METRC and cannot be used in any form without the expressed permission of the Principal Investigators.

The PREVENT CLOT Study is funded by the Patient-Centered Outcomes Research Institute (PCORI). The study is being done 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 had a traumatic orthopaedic injury(ies) which puts you at increased risk of blood clots. Your doctor believes you need to take blood clot prevention medicine. People around the country who need to start blood clot prevention medicine after trauma are being asked to take part in this study. 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 take part in this study, we will follow up with you for up to three months after admission to the hospital for your traumatic injury. If the research team is unable to get in contact with you or someone you know, a member of the research team will review your medical record in order to record any information that is usually collected during the follow up visit.

4. HOW DOES THE STUDY WORK?

If you agree to join the PREVENT CLOT Study you will be assigned randomly, or 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 as a shot or injection.
- Treatment B: Aspirin medicine given two times a day in pill form by mouth or feeding tube.

You will get *one* of these medicines as part of your normal treatment for your injuries. If you were not in the study, your doctor would make the choice about which of these medicines you would receive. In ths study,you have an equal chance of getting either one of the treatments and the treatment you receive will be decided by chance and not by your treating physican. Deciding randomly who gets the low molecular weight heparin (Lovenox/Enoxaparin) and who gets the aspirin is the best way to find out which medicine is better at preventing blood clots. Right now, we don't know which medicine is better at preventing clots for people with traumatic injuries.

If you join the study, you will begin receiving medicine as soon as your doctors wants you to start taking medicine to prevent blood clots. Usually this is immediately after you are enrolled. When you are discharged from the hospital you will continue taking the same medicine you were assigned for however long your doctor wants. Being in the study does not affect how long you take your medicin; your doctor makes that decision based on the types of injuries you have and

any other medical conditions you may have. For example, for some types of injuries doctors may give the medicine for several weeks after patients leave the hospital. For other types of injuries people may need to take the medicine for several months.

Following discharge we would like to contact you every week. At the end of this form you will able to let us know if you prefer to be contacted weekly by telephone call, text message or email, or not at all. These calls will come from a computerized system at the study coordinating center at Johns Hopkins. We will ask you how many times you took your medication that week and the interview will last for about 3 minutes. You will be able to let us know the best way to contact you at the end of this form. If you do not reply to these messages, a member of the study team may call you to see how things are going and if you no longer want to receive weekly contact you will be able to let the study team know at the end of the call, text or email. If you prefer you may complete a post card with a calendar telling us what days you took your medicine.

You will come back for your normal follow up clinic visit with your surgeon approximately 3 months after your hospitalization. When you come for the 3 month follow up, we will ask you to do a 15-30 minute interview for this study. You will be asked questions about how your recovery is going, your overall satisfaction with the medicine you took to prevent blood clots, and overall how much money you spent on the medicine you took to prevent blood clots. If you are not able to come back, we may contact you by telephone or email to do these interviews.

While you are in the study, a member of the research team at your medical center will also review your medical record to see if you had any blood clots or other visits related to your injury. Your medical record will also be reviewed to see if you were tested for COVID-19 and record the results of your test (positive or negative). Your COVID-19 results, along with all other information collected for the purposes of this study, will be kept confidential.

Option A: If you do not complete any study visits and the study team is unable to speak with you or someone else who knows how things are going with you, the study team will send information about you, which may include your name, data of birth, and social security number, to the study team at Johns Hopkins, where they will enter the information into a large administrative database called the Limited Access Death Master File, which maintains records of all deaths that have been recorded in the social security system. This may enable the team to determine why you cannot be contacted. Your data will not be recorded or maintained by the study team once the search is complete.

Opition B: If you do not complete any study visits and the study team is unable to speak with you or someone else who knows how things are going with you, the study team will enter information about you, which may include your name, data of birth, and social security number, into a large administrative database called the Limited Access Death Master File, which maintains records of all deaths that have been recorded in the social security system. This may enable the team to determine why you cannot be contacted. Your data will not be recorded or maintained by the study team once the search is complete.

The PREVENT CLOT study protocol is the confidential intellectual property of the PREVENT CLOT Principal Investigators, Steering Committee, and the University of Maryland Baltimore and METRC and cannot be used in any form without the expressed permission of the Principal Investigators.

5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

This study is comparing two widely used medicines. Each of these medicines has benefits; each also has some risks.

The risks of taking either medication are as follows:

- **Risks of Treatment A (Low molecular weight heparin (Lovenox/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.
- **Risk of 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 Reyes syndrome in younger partitipants during influenza season. Symptoms of Reyes syndrome include: fever, lack of energy or interest in things, sleepiness, changes in personality, vomiting or diarrhea.

The following symptoms are uncommon but extremely serious risks that can be associated with these medication. If you experience any of the following risks you should immediately go to the nearest emergency room:

Signs of bleeding, includingvomiting 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 dizzinessFainting, Fall or head injury, Confusion, Severe headache, Burning or numbness feeling or loss of strength. Signs of significant allergic reaction, including (wheezing, chest tightness, fever, itching, tight cough; change in skin color; seizures or swelling of face, lips, tongue or throat.)

If any of those happens, we would appreciate your also letting the study team know as well, once you are stable and feel better.

6. WHAT ARE THE POTENTIAL BENEFITS?

Patients after trauma need a medicine to prevent blood clots. You will get a medicine that will prevent blood clots in this study. Beyond that, you will not benefit from being in this study, but your being in this study will help us learn, for patients in the future with trauma, which of the two medicines works best for preventing blood clots.

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

The PREVENT CLOT study protocol is the confidential intellectual property of the PREVENT CLOT Principal Investigators, Steering Committee, and the University of Maryland Baltimore and METRC and cannot be used in any form without the expressed permission of the Principal Investigators.

You will receive $20 in recognition of your time and effort after completing the 3 month visit in person, over the phone or by email.

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

All charges associated with your treatment will be billed to you or your insurance. There are no increased costs for taking part in this research study. The costs of your usual medical care are not covered by the study but will be billed to your insurance or to you, just as usual.

9. WILL MY INFORMATION BE KEPT PRIVATE?

The information we collect from you will be kept private to the best of our ability. We will be collecting information about any treatment you received in the hospital and after you leave the hospital, and asking you questions about your recovery. Your name, birth date, medical record number and any other information that could identify you will not be recorded on these data collection forms. Instead, we will label your forms with a unique study number. The information we collect on a weekly basis through the phone calls, texts, or emails, will be stored in a separate database. We will link the information between these two databases using only the 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, and without names. That way, 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?

Your name and the phone number and/or email you provide will be shared with investigators at the data coordinating center at the Johns Hopkins Bloomberg School of Public Health if you choose to participate in this part of the study. This information will be stored separately from all study data, and will be used only for reaching out to you to see how things are going with taking your medicine every week. After your participation is the study is complete, we will destroy this information.

We will use the information we collect from you only for the purposes of this study. Large groups of data from the study may be published. You will never be identified by name. People from each participating research institution may look at 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 the group funding this study. Our funder and the ethics committee (IRB) are also allowed to look at research records if they believe it will help protect the people in the study.

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 and you will still receive blood clot prevention medicine. Your doctor will make the choice of what medicine to give you.

You may also participate in the study and choose not to participate in the weekly calls. This will not affect any other part of your participation in the study.

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.

You may choose to stop participating in the weekly contact at any time, and it will not affect your participation in the overall study.

Your participation in this research study could be ended by the researchers, either because the study is ending early or for 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 you were part of 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.

The PREVENT CLOT study protocol is the confidential intellectual property of the PREVENT CLOT Principal Investigators, Steering Committee, and the University of Maryland Baltimore and METRC and cannot be used in any form without the expressed permission of the Principal Investigators.

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

Please let us know what way you would like to be contacted and which way your prefer.

Which methods may we use to contact you? (check all that apply):	**What is your preferred communication method?**
☐ **Phone call**	☐
☐ **Text message**	☐
☐ **Email**	☐
☐ **Mail**	☐
☐ **I do not want to be contacted weekly**	

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.

The PREVENT CLOT study protocol is the confidential intellectual property of the PREVENT CLOT Principal Investigators, Steering Committee, and the University of Maryland Baltimore and METRC and cannot be used in any form without the expressed permission of the Principal Investigators.

_____ _____ _____

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