**Manual of Procedures**

for

**Comparative Effectiveness of Pulmonary Embolism Prevention after HiP and KneE Replacement:  
Balancing Safety and Effectiveness**

*The PEPPER Trial*

PCORI Protocol Number: PCS-1402-09328

Version 2.0

September 22nd, 2017





**Chapter/Appendix Version Tracker**

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# INTRODUCTION TO THE MANUAL OF PROCEDURES

## Purpose

This Manual of Operations (MOP) has been compiled by the Principal Investigator (PI) and Clinical Coordinating Center (CCC) to facilitate consistency in protocol implementation and data collection across study sites.

The MOP aims to:

* Transform the PEPPER protocol into an operational research project;
* Document study flow so that the screening, enrollment, randomization, treatment, and follow-up of all study participants are conducted in a structured and standardized manner;
* Detail how the data are observed, collected, and recorded;
* Specify quality control procedures; and
* Define methods for ensuring confidentiality of participating patient information.

## Maintenance and Distribution of the Manual of Procedures

The MOP is a living document that will be maintained and updated throughout the study by the CCC to record amendments to the protocol or informed consent form, and to document procedure changes, refinements or clarifications. Amendments will be summarized at the beginning of this document, and new versions of the MOP will be made available as soon as practicable. Clinical Sites will be notified by email when there are changes to the MOP and will be directed to the secure area of the [PEPPER website](http://www.muschealth.org/pepper/index.html) where an electronic copy will be available for download. Email “blasts” and other general study information will be sent from the dedicated PEPPER email address, [pepper@musc.edu](mailto:pepper@musc.edu). Unless otherwise noted, changes to the MOP become effective upon notification to the sites. All previous versions will be electronically archived by the CCC.

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# STUDY OVERVIEW



## Protocol Synopsis

|  |  |
| --- | --- |
| Protocol Title | Comparative Effectiveness of Pulmonary Embolism Prevention after HiP and KneE Replacement: Balancing Safety and Effectiveness (PEPPER) |
| Primary Criterion for Inclusion | Undergoing elective primary, revision, or second stage re-implantation total hip replacement, or undergoing elective primary, revision, or second stage re-implantation total or uni-compartmental knee replacement. |
| Primary Aims | 1. To compare the frequency of the aggregate primary clinical endpoints of important venous thromboembolism (clinical PE and DVT leading to hospital readmission) and all-cause mortality (aggregate indicator of fatal events, including both PE and major hemorrhage related to anticoagulant use) among three different venous thromboembolism (VTE) prophylaxis regimens. 2. To compare the frequency and nature of bleeding complications (major, clinically important, and wound-related) leading to wound drainage, reoperation, deep infection, or myocardial infarction among three different VTE prophylaxis regimens. 3. To compare the VTE prophylaxis regimens with respect to patient-reported outcomes in order to assess their impact on specific function of the replaced joint as well as general patient well-being. |
| Secondary Aims | 1. Analysis of the contribution of “standard of care” methods of anesthesia on clinical effectiveness of three different prophylaxis regimens. 2. Analysis of the relative frequency of thromboembolic events and bleeding complications between hip and knee replacement patients with each of the three regimens. 3. To compare patient preferences and risk tolerances (represented by the Patient Advisory Board) with those of physician and investigator stakeholders (Steering Committee minus patient members) to contrast two potentially disparate stakeholder perspectives. |
| Study Design | Large, randomized, pragmatic |
| Treatment Regimens | Aspirin vs. warfarin (Coumadin) vs. rivaroxaban (Xarelto) |
| Route of Administration | Oral |
| Dose and Interval | *Aspirin group*: Enteric coated aspirin (162 mg po) will be administered on the day of operation, prior to surgery, with a sip of water. Thereafter, starting on postoperative day #1, all patients in the aspirin group will receive 81 mg po bid to complete the treatment period of 30 days. Patients on preoperative cardiac dose aspirin may continue their usual dosing regimen prior to the morning of surgery, and then commence the PEPPER trial aspirin dose of 81 mg po bid on the day after operation.  *Warfarin group*: Warfarin will be administered starting on the day of operation, prior to surgery. The initial dose will be empirically determined by body weight: less than 125 lbs (56.7 kg) – 2.5 mg; 125-250 lbs (56.7-113.4 kg) – 5 mg; greater than 250 lbs (113.4 kg) – 7.5mg. The initial dose will be repeated on the evening of surgery if the preoperative dose was administered prior to noon on the day of operation; no warfarin will be given on the evening of surgery if the preoperative dose was received after noon on the day of operation. Thereafter, starting on postoperative day #1, warfarin will be given each evening based on INR values to achieve a target of 2.0 (range 1.7-2.2).  *Rivaroxaban group*: Rivaroxaban 10 mg will be first administered approximately 24 hours after completion of surgery. Medication will then be administered in the evening on postoperative day #2 and thereafter each evening until completion. |
| Duration of Study Participation | Patients will be enrolled prior to surgery and complete their participation approximately 6 months after surgery. |
| End of Study Definition | All participants have completed all follow-up visits, data collection and analysis are complete, dissemination of results and final report. |
| Number of Participants | 25,000 |
| Number of Sites | 25 |

## Specific Aims

### Primary Aims

1) *To compare the frequency of the aggregate primary clinical endpoints* of important venous thromboembolism (clinical PE and DVT leading to hospital readmission) and all-cause mortality (aggregate indicator of fatal events, including both PE and major hemorrhage related to anticoagulant use) among three different venous thromboembolism (VTE) prophylaxis regimens. An audit of all hospital readmissions within 6 months of operation will be accomplished by routine postoperative follow-up through a mechanism of central telephone surveillance of patient-reported outcome events that is augmented by on-site research coordinator follow-up and validation of suspected endpoint events and adverse outcomes.

2) *To compare the frequency and nature of bleeding complications* (major, clinically important, and wound-related) leading to wound drainage, reoperation, deep infection, or myocardial infarction among three different VTE prophylaxis regimens. Bleeding complications are defined below and will be weighted relative to other events by the Patient Advisory Board.

3) *To compare the VTE prophylaxis regimens with respect to patient-reported outcomes* in order to assess the impact of outcome events and adverse events on specific function of the replaced joint as well as general patient well-being. Validated functional outcome tools will be compared among patients with and without primary endpoint events, as well as with historical baseline data warehoused in the FORCE registry, a national AHRQ funded joint replacement outcomes database.

### Secondary Aims

a) *Analysis of the contribution of “standard of care” methods of anesthesia on clinical effectiveness of three different prophylaxis regimens.* Stratification and subgroup analysis between patients with general compared with regional neuraxial (spinal/epidural) anesthesia will assess contribution of anesthesia to efficacy of VTE prophylaxis.

b) *Analysis of the relative frequency of thromboembolic events and bleeding complications between hip and knee replacement patients with each of the three regimens.* Evidence suggests etiology of venous thromboembolic disease (VTED) differs between THA and TKA and each may warrant a distinctive prophylaxis regimen based on mechanism of action and differences in outcomes.

c) *To compare patient preferences and risk tolerances (represented by the Patient Advisory Board) with those of physician and investigator stakeholders* (Steering Committee minus patient members) to contrast two potentially disparate stakeholder perspectives. Understanding discordant patient-physician goals and risk tolerances will best serve the use of shared decision making to support choice of optimal VTE prophylaxis, as appropriate.

## Significance

Our purpose is to fill existing knowledge gaps in order to improve health care and outcomes after hip and knee replacement by providing needed evidence to better inform patient and surgeon decision-making around the choice of drug regimen for prevention of VTE and PE after total hip and knee replacement. Given the failure of current guidelines to endorse a “best practice” based on the inadequacy of clinical and health outcomes data, as well as insufficiently prior studies, there is great opportunity for this study to make a substantial difference for the large population currently undergoing hip and knee joint replacement.

The trial will assist patient and physician anticoagulant choice by informing those decisions with comparative data about the potential benefits (effectiveness) of preventing VTE, PE, and death and the related harms (safety) of perioperative bleeding and the resulting risk of compromised joint function, reoperation, deep infection, and loss of the joint replacement.We will accomplish this by a patient-centered assessment of comparative safety and effectiveness of the three most commonly employed agents for VTE prophylaxis (aspirin, warfarin, and rivaroxaban) considered along a spectrum of risk tolerance for adverse events. These events will be aggregated into five groups by type and severity: all-cause mortality; symptomatic DVT and/or PE; bleeding leading to delayed wound healing, pain, and joint dysfunction; reoperation to drain a collection of blood from the wound; and infection resulting in implant removal. To elucidate the tradeoff between preventing PE death and avoiding treatment-related morbidity, we will analyze patient-reported outcomes to assess the impact of adverse events on joint-specific function and overall health and well being. Patient preferences and risk tolerance will inform the decision that must be made regarding choice of prophylaxis for PE after total joint replacement. No study to date has been designed to consider the offsetting *benefits* of preventing PE death against the *harms* of postoperative bleeding, reoperation, infection, and loss of function that are associated with VTE prophylaxis. Likewise, no clinical trial has been adequately powered to concurrently assess both safety and effectiveness of VTE prophylaxis, particularly as safety relates to the patient-perceived morbidity of bleeding and its long-term consequences. Because currently employed drugs vary widely in strength of anticoagulant effect, it is critical to define the risks and benefits of each to guide patients and stakeholders in this important decision. The proposed clinical trial will provide specific information regarding competing *benefits* and *harms* of VTE prophylaxis that balance effectiveness and safety based on a patient-perceived value proposition of functional outcomes.

There is a strong likelihood that information derived from this trial would inform patients and other stakeholders in such a way that will quickly catalyze significant changes in current practice with immediate benefit accrued to patients and the healthcare system. Evidenced by informal polls at recent professional meetings and uncertainty in some centers about randomizing patients for this trial, increasing numbers of orthopaedic surgeons have evolved to aspirin as their preferred strategy for VTE prophylaxis. This migration is likely attributable to aspirin’s perceived low rate of clinical PE and favorable bleeding profile in comparison to newer anticoagulants. The same polls also suggest an increase in use of rivaroxaban over low molecular weight heparin, likely driven by its striking reduction in venographic clot rates coupled with the convenience of a pill over the need for injection. Warfarin remains preferred by 30-50% of surgeons due to its effectiveness, familiarity, and favorable safety profile with low rates of perioperative bleeding. These recent changes in prophylaxis preference suggest that current practice patterns are not well established and would likely respond quickly to new data and/or changes in clinical guidelines. If rivaroxaban is found to be only modestly, or not at all, superior to warfarin or aspirin in preventing *clinical* VTE and PE, or is accompanied by a substantial increase in bleeding, the latter agents may be considered more desirable by some or even deemed to be clearly superior in VTE prophylaxis. This situation would rapidly lead to increased use of less intensive anticoagulation after hip and knee replacement and would undoubtedly reduce the occurrence of bleeding-related complications and improve functional health outcomes. Parenthetically, if aspirin or warfarin became more widely adopted as less intensive anticoagulation strategies that were not inferior to rivaroxaban in VTE/PE prevention, substantial cost savings would accrue to the health care system. Annual drug cost savings alone would account for more than $250 million, based on 35 days of rivaroxaban prophylaxis for 1 million THA and TKA performed in the US each year. A substantial quality benefit would also accrue to society from a reduction in bleeding events and reoperations that result in prolonged convalescence and disability. Conversely, were rivaroxaban found to be substantially more effective in preventing VTE/PE with no increase in bleeding risk, its rapid endorsement as the preferred prophylaxis could be anticipated along with reduced mortality related to PE. Therefore, regardless of the findings, our clinical trial will substantially improve quality of care for *individual* patients by defining a balance between prevention of clinically meaningful VTE and the risk of adverse bleeding and disability. We predict that such a patient-centric approach to optimal VTE prophylaxis will, at least in some patients, result in selection of less intensive anticoagulation regimens that place greater value on avoidance of morbidity associated with bleeding.

## Study Design

This large randomized pragmatic clinical trial aims to study event rates for benefits (effectiveness) and harms (safety) endpoints associated with the three most commonly employed VTE prophylaxis regimens representing the current spectrum of clinical orthopaedic practice in North America. Our hypothesis is that prevention of clinically meaningful venous thromboembolism (VTE: PE and DVT) and death after total hip and knee replacement with aspirin or low intensity warfarin (INR 2.0) *will not be inferior to* rivaroxaban, a direct factor Xa inhibitor that significantly reduces venographic thrombosis rates, and will be associated with fewer late consequences of adverse bleeding, such as reoperation, infection, and myocardial infarction, that compromise patient reported outcomes related to long term joint-specific function and general well-being. All patients will utilize in-hospital mechanical compression devices in accordance with local standard practice. The study design and approach of this large pragmatic clinical trial balance generalizability and internal validity with a design (randomized, three-group parallel design and analysis) that sets standards for internal validity and approach (few exclusion criteria, large number of geographically diverse clinical sites, simple and commonly used treatments administered as best possible with local resources, treatment administration and follow-up in community settings, patients living in the community under no unusual social constraints, outcomes that are big medical events based on death or hospitalization that are easily recognizable and of importance to patients, and no collection of non-essential data) and enhances generalizability. Inclusion criteria are broad, extending to virtually all patients 21 years of age or older undergoing primary or revision hip or knee replacement. Concomitant patient care is at discretion of individual treating surgeons, and follow-up visits are scheduled according to the surgeon's routine and clinical indications only.

The total study period will encompass 4½ years: 6 months for preliminary work; 36 months of patient enrollment; 6 months trailing follow-up after closure of enrollment; and 6 months for final data analysis. Each site will enroll approximately 1,000 patients over three years for an average annual site enrollment of 333 patients. Overall study enrollment targets are detailed in [Appendix B: Cumulative Target Enrollment](#_Appendix_B:_Cumulative). With anticipation of no more than a 10% rate of loss to follow-up, which is a conservatively high number in this elective patient population with customary lifetime follow-up, the study will result in 22,500 evaluable patients with complete follow-up after an index operation. Nevertheless, a concerted and proactive effort will be required to capture outcome assessment data consistently at the pre-specified time points. We will recruit patients locally within the geographic region of each participating institution to the practices of all participating surgeons in those institutions. Regional advertisement of the trial will assist in recruitment as will the fact that the trial involves only FDA approved drugs endorsed by current clinical guidelines without use of any “experimental” agents. National patient advocacy organizations involved as stakeholders in the trial will assist in publicizing trial recruitment and results.

**Recruitment Plan**

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| Total number of study participants expected to be screened across approximately 25 sites: | 112,650 |
| Of those screened, total number of study participants expected to be eligible (90%): | 101,385 |
| Target enrollment (22% of screened) | 25,000 |
| Target sample size with complete follow-up (accounting for 10% loss to follow-up): | 22,500 |

## Project Timeline and Major Activities

The initial 6 months of the 4½ year trial will be devoted to the constitution of the key centers and committees responsible for overseeing the study, including the Clinical and Data Coordinating Centers (CCC and DCC), Steering Committee (SC), Outcomes Assessment Committee (OAC), Data and Safety Management Board (DSMB), and the Patient Advisory Board (PAB). This period will serve to confirm definitions and tasks, and then sequential committee meetings will continue every 6 months until review of final datasets for the last enrolled patients. The study protocol and ICF will be developed and approved by the IRB and distributed to the clinical sites. The CCC will provide support to the clinical sites utilizing MUSC’s Central IRB, and confirm the adoption/approval by local IRBs where necessary. Initial meetings of the SC, PAB, and the study “kick-off” meeting of clinical site PIs and research coordinators will be held. The DSMB will provide approval of the protocol and the DSMB Charter, including criteria for pausing or stopping the study.

Patient enrollment will begin in the 7th month and continue for 36 mos, through the 42nd month of the project. Patient data collection will commence with enrollment of patients and continue for 6 months after enrollment of the last patient; data will be collected on each patient at enrollment, hospital discharge, and approximately 1 month, 3 months, and 6 months after operation. Collection of final endpoint data for each patient will occur at 6 months postoperatively.

The PAB will continually review and analyze conjoint analysis data on risk tolerances as well as follow-up data throughout the project, provide their findings and analysis to the OAC in time for review of outcomes and adverse events, and the OAC will provide their analysis to the DSMB for review, assessment, and report. This sequence of audit and analysis will recur every 6 months in support of ongoing semi-annual DSMB reviews. Data and statistical analysis will occur continually throughout the period of the project, starting 3 months after the start of patient enrollment, and formal reports will be issued every 6 months in coordination with the PAB review as outlined. Final data and statistical analysis will occur over the last 6 project months, during manuscript preparation, in concert with the OAC, PAB, and SC collaborations. Also see [Appendix C: Project Timeline and Deliverables](#_Appendix_C:_Project).

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| **Activity** | **Projected Outcome Milestones** |
| 1. Development of policies and procedures manual, questionnaire, final study protocol | 4 months |
| 1. Clinical Coordinating Center consent development and central IRB approval | 6 months |
| 1. Study Registration at ClinicalTrials.gov | 6 months |
| 1. Commencement of patient recruitment / enrollment / intake data collection | 6 mos/on |
| 1. Central patient randomization | 6 mos/on |
| 1. Rolling monthly interim enrollment progress reports Enrollment milestones: 12 mos, 1st 25%; 9 mos, 2nd 25%; 9 mos, 3rd 25%; 6 mos, last 25% | 6 mos/on |
| 1. Rolling 3 month interim reports with web-based clinical data acquisition for each patient | 9 mos/on |
| 1. Site prep and completion of local IRB approvals; All sites enrolling – 12/1/2016 | 9 months |
| 1. Patient Advisory Board review, every 6 months, 1st and 3rd quarters | ongoing |
| 1. Outcomes Assessment Committee review / adjudication of AEs – 2nd, 4th quarters | ongoing |
| 1. Data and Safety Monitoring Board review minutes – every 6 months, 2nd, 4th quarters | ongoing |
| 1. Interim progress reports, data analysis and statistical review, semi-annual, 2nd and 4th quarters | ongoing |
| 1. Steering Committee oversight and review – monthly conference calls | ongoing |
| 1. Enrollment target, 25%\* | 15 months |
| 1. Enrollment target, 50%\* | 24 months |
| 1. Enrollment target, 75%\* | 33 months |
| 1. Close of patient enrollment, 25,000 patients | 42 months |
| 1. Final patient clinical follow-up | 48 months |
| 1. Patient Advisory Board: weighted event review; analysis of relative risk tolerances | 51 months |
| 1. Final data collection, review, and final analysis | 51 months |
| 1. Information dissemination, final report, and manuscript preparation | 54 months |
| 1. Manuscripts accepted for publication | 60 months |
| 1. De-identified datasets and sharing per plan; within 9 mos of project close | 63 months |

# ADMINISTRATION



## Study Leadership Structure

### Organizational Chart

Clinical Sites

N=25

Data & Safety Monitoring Board

(overall study safety)

Patient Advisory  
Board

(risk tolerance analysis)

Clinical Coordinating Center

(enrollment monitoring,  
clinical site support)

Data Coordinating Center  
(data analysis, DSMB reports)

**Steering Committee**

(overall study performance)

Outcomes Assessment Committee

(S/AEs adjudication)

*Axio Research*

(DSMB reports)

*Statix*

*(Data collection  
& randomization)*

**Executive Oversight Committee**

(operational oversight)

### Roles and Responsibilities

|  |  |  |
| --- | --- | --- |
| **Name** | **Role on study** | **Contact Information** |
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| **Carol A. Lambourne, MSc, PhD**  Department of Orthopaedics  Medical University of South Carolina | National Project Manager | 96 Jonathan Lucas Street, MSC 622 Charleston, SC 29425  Phone: 843-792-2913  lambourc@musc.edu |
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### Steering Committee

The Steering Committee (SC) is responsible for overseeing the study. This committee will make major organizational and policy decisions. The committee, chaired by the Principal Investigator (PI), is the governing body for the project and will meet in person on a semi-annual basis to dispatch issues that require decision. Urgent matters will be addressed by conference call. The SC will oversee protocol refinement prior to implementation and monitor patient enrollment, individual site performance, milestone accomplishment, and work of the committees and coordinating centers. Key members and their roles include:

|  |  |  |
| --- | --- | --- |
| Vincent Pellegrini, MD | PI | Director, Clinical Coordinating Center |
| Larry Magder, PhD | Co-I | Director, Data Coordinating Center |
| Samuel Z. Goldhaber, MD | Co-I | Chair, Outcomes Assessment Committee |
| Roger Bulger, MD | Co-I | Co-Chair, Patient Advisory Board; TKA patient |
| C. McCollister Evarts, MD | Co-I | Co-Chair, Patient Advisory Board; THA patient |
| John Eikelboom, MD | Co-I | Expert in thrombosis and aspirin effects |
| Patricia Franklin, MD | Co-I | Expert in PROs |
| Jay Magaziner, PhD, MS | Co-I | Research Representative, Epidemiology & Biostatistics |
| Kevin Garvin, MD | Co-I | Research Representative, The Knee Society |
| Richard Iorio, MD | Co-I | Research Representative, The Hip Society |
| Leslie Lenert, MD | Co-I | Facilitator, Patient Advisory Board |
| Kathryn Mikkelsen | Stakeholder | North American Thrombosis Forum |
| Teresas Bordeaux | Stakeholder | National Blood Clot Alliance |
| Lisa Moores, MD | Stakeholder | American College of Chest Physicians |

## Executive Oversight Committee

The Executive Oversight Committee (EOC) meets by teleconference on a weekly basis to review operational details and ongoing timelines for efficient progress of the study.

## Coordinating Centers

### Clinical Coordinating Center

The Medical University of South Carolina, Department of Orthopaedics will be responsible for clinical coordination of the trial, under the direction of the PI. The responsibilities of the Clinical Coordinating Center (CCC) are:

* Identification and contracting of clinical sites;
* Provide administrative and fiscal support for the clinical sites;
* The planning and arrangement of committee meetings (Patient Advisory Board, Outcomes Assessment Committee, Data and Safety Management Board, Steering Committee) and annual meetings of site investigators and coordinators;
* Maintenance of website [www.muschealth.org/PEPPER](http://www.muschealth.org/PEPPER), ensuring all study documents (reports, forms, etc.) available for download are up to date;
* Establishment and administration of Central IRB residing at MUSC, and secure Reliance Agreements from sites using the Central IRB;
* Obtain approval for the study Protocol, Informed Consent Form/HIPAA, and other regulatory documents. Ensure all clinical sites are informed of amendments to regulatory documents and provide assistance to facilitate maintenance of approval;
* Assist clinical sites in matters concerning recruitment, protocol adherence and data collection;
* Monitoring of enrollment and overall site performance;
* Plan and conduct site visits;
* Reconciliation and payment of all invoices and other costs related to the trial;
* Preparation and submission of regular progress reports to PCORI;
* Oversight of data analysis and preparation of manuscripts related to the trial; and
* In collaboration with the Data Coordinating Center (DCC) lead presentation and publication of study results for scientific and lay audiences.

### Data Coordinating Center

The Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, will be responsible for data coordination of the trial under the oversight of Lawrence Magder, PhD. The responsibilities of the Data Coordinating Center (DCC) are:

* Receipt and organization of data files from Statix;
* Cleaning and editing of data files for analysis;
* Preparation of reports for the Steering Committee, Executive Oversight Committee, Data and Safety Monitoring Board, Outcomes Assessment Committee, and Patient Advisory Board;
* Perform all interim and final analyses;
* Contribute to the authorship and dissemination of study results to scientific and lay audiences.

## Partners

### Axio Research, LLC

Axio Research is a provider of biostatistics and data management services to the clinical research community. Axio will collaborate with both Statix and the DCC to design and prepare periodic reports to the DSMB and undertake an audit of the randomization system.

### Statix, LLC

Statix, LLC is a centralized website design and data collection and hosting service directed by Brook Martin, MPH, PhD, an expert in health services research and bioinformatics. Dr. Martin is an adjunct Associate Professor at the Utah, Department of Orthopaedics. Statix will serve as the primary centralized data base for electronic data capture and provide a centralized automated randomization system with appropriate security and firewalls from the data base capture function.

## Clinical Sites

At each collaborating clinical site, a primary investigator and site coordinator will be identified who will work closely together to assure successful performance of the trial. Clinical sites are expected to enroll a minimum of 1,000 patients each during the three year recruitment period (25 clinical sites x 1,000 patients/clinical site = 25,000 patients). Clinical sites in the PEPPER trial are subject to change according to the feasibility of study conduct at each site.

### Roster of Clinical Sites

|  |  |
| --- | --- |
| **Institution** | **PI** |
| Anderson Orthopaedic Institute | Kevin B. Fricka, MD |
| Arthritis Surgery Research Foundation, Miami | Carlos J. Lavernia, MD |
| Cleveland Clinic | Michael A. Mont, MD |
| Dartmouth-Hitchcock Medical Center | Wayne E. Moschetti, MD |
| Duke University Medical Center | Michael P. Bolognesi, MD |
| Geisinger Health Center | Michael Suk, MD JD MPH |
| Johns Hopkins University | Robert S. Sterling, MD |
| Lahey Clinic | Michael S. Kain, MD |
| London Health Sciences Centre Research | Brent Lanting, MD |
| Mayo Clinic – Scottsdale | Mark Spangehl. MD |
| Mayo Clinic – Rochester | Kevin I. Perry, MD |
| Medical University of South Carolina | Richard J. Friedman, MD |
| Midwest Orthopaedics at RUSH | Scott M. Sporer, MD |
| New York University | Richard Iorio, MD |
| Penn State Hershey Med Center | Charles M. Davis, MD PhD |
| Sinai Hospital, Baltimore | James Nace, DO MPT |
| Stanford University Hospital | William J. Maloney, MD |
| University of Arkansas for Medical Sciences | C. Lowry Barnes, MD |
| University of California, Los Angeles | Bert J. Thomas, MD |
| University of Nebraska | Kevin L. Garvin, MD |
| University of Pennsylvania | Charles Nelson, MD |
| University of Virginia | James A. Browne, MD |
| University of Washington | Navin D. Fernando, MD |
| Virginia Commonwealth University | William A. Jiranek, MD |
| West Virginia University | Brock Lindsey, MD |

### Clinical Site Principal Investigators

The responsibilities of the Clinical Site PI include:

1. Conduct the study in accordance with the current protocol, knowingly deviating from the protocol only when it is necessary to protect the safety, right and welfare of study participants;
2. Ensure that all personnel participating in the conduct of the study are informed of their obligation to carry out the responsibilities as listed above;
3. Ensure that all orthopaedic surgery staff involved with the care of patients with total hip or knee joint replacements are well informed about the trial;
4. Ensure all patients needing a total hip or knee joint replacement are routinely considered for the trial;
5. Ensure that the treatment assignment is followed;
6. Communicate with Clinical Coordinating Center staff and Data Coordinating Center staff about any problems or concerns related to the study;
7. Resolve all queries as requested;
8. Report any adverse events experienced by participants during the study promptly and in adherence with protocol guidelines;
9. Make no changes in the research activity without IRB approval, except in instances when an immediate hazard to study participants is present;
10. Assist the Clinical Site Coordinator as necessary;
11. Comply with all obligations and requirements of Clinical Investigators in accordance with 21 CFR Part 312 and to comply with all IRB, state and federal regulations for human research, including guidelines found in the Manual of Procedures;
12. Ensure that all study personnel have read the protocol and clearly understand his/her responsibilities;
13. Ensure all study personnel have been trained in order to meet study guidelines and have signed the protocol training log indicating they understand their responsibilities as assigned; and
14. Participate in Steering Committee meetings and other committees if requested to do so.

### Clinical Site Coordinators

The responsibilities of the Clinical Site Coordinator include:

* 1. Identify all eligible total hip or knee joint replacement patients for the trial;
  2. Obtain informed consent from the patient if not obtained by the clinical site lead investigator or other investigators;
  3. Enroll the participant in the study using a web-based randomization application;
  4. Inform surgeons and nurses caring for the participant of the participant’s randomization and document same;
  5. Completion of data collection forms and process data edit queries;
  6. Ensure compliance with the study protocol;
  7. Perform or delegate to trained staff at the clinical site the entry of data from the forms in to the web-based electronic data capture (EDC) system and arrange for copying and mailing of medical records to the CCC for quality assurance, if required;
  8. Report any eligible adverse events in the EDC system, and collect and upload appropriate medical records per Adverse Event Reporting guidelines ([Section 8. Safety Assessments and Reporting](#_SAFETY_ASSESSMENT_AND));
  9. Respond to requests for confirmation of Adverse Event reporting from the CCC and Statix, and upload appropriate supporting medical records and documentation into the database;
  10. Train assistant site coordinator(s) and other staff at the clinical site as needed; and
  11. Adhere to all guidelines governing clinical research.

## Patient Advisory Board

The Patient Advisory Board (PAB) comprises ten hip or knee replacement patients in addition to a physician expert in the study of patient preferences, who will facilitate proceedings of the PAB. The Patient Advisory Board (PAB) will assist in formulating methods of study design and techniques for data collection as well as strategies for critical determination and analysis of patient-perceived relative importance of the observed study findings.

In addition to consultation in study design and promotion of the trial, the PAB will provide analysis of the relative importance of primary safety and effectiveness endpoints from the patient’s perspective. Specifically, the PAB will formulate a relative weighting of pre-operative patient risk aversion for VTE and fatal PE compared with adverse bleeding and attach a patient-perceived value to the avoidance of each. They will then process this conjoint pre-operative patient risk analysis together with the patient reported outcomes for joint function and overall health from study participants experiencing primary outcome events in each of the three study arms. This will result in an overall preference weighting of each prophylaxis regimen based on observed benefits and harms. Finally, the PAB will provide an independent review of final study results and event rates associated with each prophylaxis regimen relative to the frequency of observed harms and benefits and patient preferences for each. The patient advisory board will therefore provide a unique assessment of primary study endpoints and patient reported outcomes from a patient-centric perspective; that review will then be juxtaposed to a traditional scientific analysis of the full steering committee and these two perspectives will be considered in formulating a final interpretation of the study outcomes. In this manner, both the participants in the trial as well as the PAB will inform the interpretation and analysis of data with the patient’s perspective on risk tolerance for adverse events.

## Outcomes Assessment Committee

The Outcomes Assessment Committee (OAC) will review and validate outcomes on an ongoing basis during the course of the trial and adjudicate adverse events based on blinded event reports and supporting documentation received from the CCC.

See Section [8.2 Outcomes Assessment Committee](#_Outcomes_Assessment_Committee) for additional information about the reporting and adjudication of adverse events.

## Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will monitor accruing data to assure that patients in the clinical trial are being cared for safely, based on summaries of serious or unexpected adverse events adjudicated by the Outcomes Assessment Committee. They will meet by semi-annual teleconference or in-person meetings to evaluate safety for the purposes of approving or disapproving continuation of the clinical trial. See section [8.3 Data and Safety Monitoring Board](#_Data_and_Safety) for additional information about the DSMB’s responsiblities and activities.

# COMMUNICATIONS PLAN



In person meetings, conference calls, e-mail, specified scheduled reporting, and telephone will be used to maintain frequent and regular communications between the Executive Oversight Committee (EOC), Steering Committee (SC), Clinical and Data Coordinating Centers (CCC and DCC), Clinical Sites, Patient Advisory Board (PAB), Outcomes Assessment Committee (OAC), Data and Safety Monitoring Board (DSMB), and the Patient Centered Outcomes Research Institute (PCORI).

Clinical sites are encouraged to use the [PEPPER website](http://www.muschealth.org/pepper) where study resources are avilable, as well as the study-specific email address [pepper@musc.edu](mailto:pepper@musc.edu) to communicate with the CCC.

The PI, CCC team, and lead study investigators will meet weekly or as needed by teleconference/WebEx to review study progress and protocol adherence at the participating clinical sites, review committee activities, and plan study meetings.

The SC will meet alternately by teleconference and in person on a semi-annual basis to review the work of the committees and coordinating centers, and monitor overall study performance and progress towards patient enrollment goals.

The CCC will:

* Plan semi-annual, in-person meetings for the PAB, OAC, and DSMB on a rolling basis throughout the study;
* Plan annual Investigator Meetings throught the period of data collection;
* Maintain the [PEPPER website](http://www.muschealth.org/pepper/index.html) and a study-specific email account ([pepper@musc.edu](mailto:pepper@musc.edu)) for communication and distribution of information/resources with the clinical sites;
* Monitor site-specific and overall patient enrollment and disseminate performance metrics to the sites on a monthly basis via the [PEPPER website](http://www.muschealth.org/pepper/index.html), in accordance with the [Site Monitoring Plan](#_SITE_MONITORING_PLAN);
* Conduct weekly conference calls with the DCC on an ongoing basis to discuss methodological and analytic issues;
* Communicate with the clinical sites on an as needed basis to provide guidance on operational matters, including investigator and coordinator training;
* Collect and organize adverse event-related supporting documentation and forward these to the OAC for adjudication;
* Prepare and submit study progress reports to PCORI on a semi-annual basis, in addition to other study-related documents as contractually required; and
* Lead manuscript preparation efforts in collaboration with the DCC.

The DCC will:

* Provide methodological and analytical expertise to the PI, EOCommittee, and SC throughout the duration of the study;
* Attend semi-annual SC meetings and weekly teleconference meetings of the EOC;
* Receive data from Statix and Axio on a regular basis for interim analyses and preparation of DSMB reports;
* Support and collaborate in the final study analysis; and
* In collaboration with the CCC contribute to manuscript preparation efforts.

The Clinical Site PIs and coordinators are expected to communicate on an on-going basis by telephone, email, and/or in person to review study operations and progress, and address any barriers to successful patient enrollment. The lead coordinator is responsible for overseeing and documenting the training of all site investigators and secondary/tertiary coordinators in the protocol and operational procedures (see section [5. Site Preparation](#_SITE_PREPARATION)).

# SITE PREPARATION



## PEPPER Website

The dedicated PCORI PEPPER website serves as a resource for patients and clinical site research teams, and is available at [www.muschealth.org/pepper](file:///\\db\db5\Ortho%20PCORI%20Pepper\PCORI\MOP\www.muschealth.org\pepper). The site includes a publicly-viewable home page containing general study information including participating clinical sites, as well as links to the National Clinical Trial study profile on [www.clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT02810704?term=pellegrini&state1=NA%3AUS%3ASC&rank=1), and the [PCORI project summary](http://www.pcori.org/research-results/2015/comparative-effectiveness-pulmonary-embolism-prevention-after-hip-and-knee). PEPPER resources including regulatory documents, study forms, and Investigator meeting presentations are avilable to authorized site investigators and coordinators in a secure password-protected area of the site. This will also be the location of site-specific performance metrics and overall study progress, which will be posted on a monthly basis.

## Electronic Data Capture

Statix has developed a PEPPER-specific central electronic data capture system for data collection from all clinical sites. The system contains a series of “forms”, analogous to the paper forms and survey instruments used by coordinators during the course of the study, which are completed in sequence as the patient progresses from pre-screening through screening, randomization, surgery, and hospital discharge. The system also contains the follow-up instruments to be completed by Statix staff in the conduct of follow-up contacts, and relevant forms for protocol deviation reporting, and the collection and adjudication of serious adverse events, including the ability to upload supporting documentation required for the OAC.

The system uses a dedicated Multisite Wordpress Application, which employs physical, electronic, and procedural safeguards to protect personal information. It is hosted on a HIPAA-compliant cloud-based Linux platform, that is professionally managed with security updates, optimized for scalability, and backups. Access to Statix’s content management system is defined by privileges based on user type, in accordance with the principles of minimum necessity, separation of duties, and least privilege. All users receive an account to update contact information and interact with a dashboard of features that depend on user type. Access to the dashboard is password protected, requiring two-step authentication and password recovery. The system automatically provides a unique identifier for each user that is used to log all transactions in an audit trail, in accordance best practices for managing research databases.

The CCC and Statix will maintain administrative rights to manage the system, and will add users as clinical sites embark upon data collection. The addition of a new user prompts the system to send an email including a link to a webpage where the user can establish a personal password. At this point, the user will be forwarded to their personal and site-specific dashboard, which provides real-time aggregate data summarizing the status of patient enrollment and survey completion, and acts as the launchpad from which they can navigate to the various functions of the system.

Preliminary training was provided to site coordinators in two live web sessions in August 2016 along with protocol training; this is available to download and view from the [PEPPER website](http://www.muschealth.org/pepper/index.html). Additional and more detailed training slides, which are updated to reflect protocol changes and refinements to the Statix database, are also available from the PEPPER website. The CCC will provide assistance in the use of the EDC system throughout the data collection period.

## Staff Training

Clinical Site PIs and Coordinators must be certified and trained in procedures of key importance to the study prior to initiation of recruitment. Initial training was performed at the first annual Investigator’s Meeting in May 2016. Two live web-based training sessions were subsequently conducted (August, 2016) for site coordinators during which a more thorough review of the study protocol was provided, including recruitment procedures, eligibility criteria, obtaining informed consent, randomization, adherence, and data collection and reporting procedures including use of the EDC system. These sessions also provided coordinators with an introduction to the Central IRB and a PEPPER website overview. Training slides and a recording of one of webinars, in addition to a list of questions and answers (“Q&As”) generated from coordinator responses during and after the training sessions are available for download on the [PEPPER website](http://www.muschealth.org/pepper/index.html). All coordinators in attendance completed the Training Completion Form following the webinar, which were returned to the CCC.

Coordinators joining site research teams after the the August 2016 webinars are required to complete the training by viewing the [webinar](https://connect.musc.edu/p66lw9urwc0), reviewing the current version of the training slides (updates are indicated), in addition to the PEPPER Coordinator Training Q&As. They must then complete the Training Completion Form, indicating the method of training as “Viewed Recording” and return this to the CCC.

The lead coordinator at each site is responsible for ensuring that his or her investigators and co-coordinators are appropriately trained to perform their responsibilities. Investigators are required to sign the PEPPER Training Log, which is retained by the sites. Amendments to the study protocol, informed consent document, EDC system, or randomization system will necessitate the completion of a new training form for all study team members. The CCC will notify clinical sites when these changes occur.

All meeting-related documents, resources, and forms referred to above are available for download from the [PEPPER website](http://www.muschealth.org/pepper/index.html).

## Delegation of Roles & Responsibilities

Clinical site PIs, sub-investigators, and coordinators are required to complete the PEPPER Delegation Log by identifying his or her role on the study, as well as their duties. S/he will enter the date on which they joined the research team, which must be certified by the PI. A termination date must be recorded on the delegation log in the event a team member is removed from the study or at completion of the trial. The delegation log should be retained by the clinical staff and filed in the regulatory binder.

Personnel responsible for administering standard of care protocols for patients enrolled in the PEPPER trial, but are *not* involved in research procedures should not sign the delegation log.

# REGULATORY ADHERENCE



## Central IRB

Clinical sites participating in PEPPER are strongly encouraged to utilize the Central IRB based at MUSC and managed by the CCC as their IRB of record, where local institutional policy permits. The Central IRB increases the efficiency with which sites can obtain regulatory approval, reduces the amount of time to approval, and reduces the administrative burden on clinical site coordinators. The IRB Liaison at the CCC is responsible for facilitating the regulatory approval of those sites able to use the Central IRB and corresponding with the IRB on matters of human subjects protections. S/he is also responsble for distributing amended approved documents and ensuring that sites are using current versions of the ICF and protocol. Where institutional policy prevents clinical sites from using the Central IRB, the IRB Liaison is also responsible for providing up to date templated regulatory documents for local approval and use.

## Protection of Human Subjects

### Informed Consent Process

Patients will be recruited to the study at each site under the approval of a centralized Institutional Review Board at MUSC, or local IRB approval of a modified document to meet local requirements. A common template for the informed consent document will be created by the CCC and provided to each site for consideration, modification, and approval as appropriate by the local IRB.

During the proposed trial, it is anticipated that informed consent will be obtained by the study site coordinator under the direction of the site PI in the outpatient setting either at the time of preadmission testing in the weeks prior to the anticipated procedure or following completion of preadmission testing after satisfying all questions and concerns of the participating patient prior to the planned operation. The consent form will describe the purpose of the study, the procedures to be followed, and alternatives to participation. Potential risks and benefits associated with study-related activities will be provided in the consent form and explained verbally to each participant during the informed consent process. Individuals will be encouraged to ask questions, will be reminded that participation in the study is voluntary, and that they may withdraw from the study at any time. Participants must demonstrate that they understand the study procedures and potential risks in order to provide their own informed consent. Proxy consent will not be allowed. A signed consent form will be obtained from each participant who meets eligibility criteria and is willing to participate in the study; this will enable the coordinator to collect baseline data and randomize participants to one of the eligible study medications.

### HIPAA Authorization

Clinical sites where patients are pre-screened for enrollment in PEPPER on the basis of medical record information prior to any patient contact must obtain local IRB waiver of HIPAA and informed consent for that medical record review. HIPAA authorization requirements are included in the template consent form provided to sites by the CCC. Local IRBs may require investigators at their clinical sites to separate the document for HIPAA authorization from the informed consent. Clinical sites that do not use MUSC as the IRB of record are responsible for providing current, approved versions of the consent form and the HIPAA authorization form to the CCC throughout the duration of the study.

### Protocol Deviations and Violations

A protocol deviation is any variance from the protocol involving one or more subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval.

Deviations range in seriousness according to how the changes may impact subject safety, the degree of noncompliance with federal and state regulations, and the degree of foreknowledge of the event. Anticipated changes to a protocol should always be reported before event occurrence unless an immediate change is necessary to protect subject safety. Repeated deviations of the same type may be an indication that an amendment is needed to permanently change study criteria. Examples of deviations may include, but are not limited to:

* Use of an invalid consent form, ie. approved consent form without IRB approval stamp or outdated/expired consent form;
* Failure to obtain informed consent, ie. there is no documentation of informed consent, or informed consent is obtained after initiation of study procedures;
* Missing original signed and dated consent form (only a photocopy available);
* Inappropriate documentation of informed consent, including:
* missing investigator signature;
* copy not given to the person signing the form;
* Enrollment of a subject who did not meet all inclusion/exclusion criteria;
* Performing a study procedure not approved by the IRB;
* Failure to report serious unanticipated problems/adverse events involving risks to subjects to the IRB and (if applicable) the sponsor;
* Study visit conducted outside of the time frame listed in the IRB-approved protocol;
* Implementation of unapproved recruitment procedures; and
* Individual obtaining informed consent not listed on IRB approved study personnel list.

For those clinical sites using MUSC as the IRB of record, the deviation must be reported to the CCC as soon as possible and no later than 5 days following its discovery. A corrective action plan must be provided. The CCC will report the deviation to the IRB as soon as it is aware of the deviation and no later than 10 working days following the original discovery. Sites may also be required to report the deviation to their local IRBs, per institutional policy. Sites not using the Central IRB at MUSC are responsible for reporting protocol deviations to their own IRB per institutional requirements, and must forward a copy of the deviation report to the CCC as soon as possible. A completed copy of the Protocol Deviation Form must be maintained in the regulatory file as well as in the subject’s source document file. The CCC will retain all submitted protocol deviation reports.

# PROTOCOL IMPLEMENTATION



## Planned Enrollment

The PEPPER site aims to enroll 25,000 patients across 25 clinical sites. Each site will enroll approximately 1,000 patients over three years for an average annual site enrollment of 333 patients, or 7 patients/week for one study coordinator working 48 weeks/year.

## Recruitment, Screening and Enrollment

All regulatory and source documents, recruitment aids, and data collection instruments referred to below are available for download from the [PEPPER website](http://www.muschealth.org/pepper/index.html).

### Pre-Screening and Recruitment

Demographic information should be collected for *all* patients of the site PI and participating surgeons scheduled for elective total hip or knee replacement using the Pre-Screening Form. This information may be gathered from the medical record by the coordinator or another member of staff authorized to view this information (eg. patient scheduler), and will provide the denominator for calculation of the estimated enrollment rate. These data should be entered into the [Statix database](https://app.gsrweb.com/musc/) database and the completed paper form kept in the study participant file.

On the reverse side of the Pre-Screening Form is the Patient Recruitment Form. This form contains the basic eligiblity criteria required to determine whether a patient should be be approached for recruitment. These data should *not* be entered into the [Statix database](https://app.gsrweb.com/musc/) database at this time.

### Screening

Patients should then be reviewed for eligibility using the Screening and Surgeon Sign Off form. If a patient is determined to be eligible for the study (see [Inclusion Criteria](#_Inclusion_Criteria) and [Exclusion Criteria](#_Exclusion_Criteria), below), physician confirmation is required and recorded on the form before the patient may be randomized.

### Inclusion Criteria

All patients attending clinic and considering elective prmary or revision total hip or total or uni-compartmental knee replacement surgery will be screened for eligibility in the study, using the following inclusion criteria:

1. Males and females 21 years of age or older;
2. Patients must be undergoing an elective primary, resurfacing arthroplasty, revision, or second stage re-implantation total hip replacement or resurfacing arthroplasty, *or* an elective primary, revision, or second stage re-implantation total or uni-compartmental knee replacement;
3. Patient has the necessary mental capacity to participate and is able to comply with study protocol requirements;
4. Patient is willing and able to give informed consent; and
5. Patient is willing and able to be randomized and participate

### Exclusion Criteria

Patients will be *excluded* from the study if they meet one or more of the following criteria:

1. Patient is undergoing bilateral hip or knee replacement;
2. Patient is undergoing a total hip or knee replacement and has been enrolled in this study for a prior hip or knee replacement;
3. Patients on chronic (longer than the prior six months) anticoagulation other than with antiplatelet medications;
4. Patient is concurrently enrolled in another active interventional clinical trial testing a drug or intervention known or believed to interact with aspirin, warfarin, or rivaroxaban;
5. Patient has a contraindication to two or more of the three study medications;
6. Women who are pregnant or breastfeeding, as well as those of reproductive potential unless there is a negative urine pregnancy test on the day of surgery;
7. Patient has a documented gastrointestinal, cerebral, or other hemorrhage within three months of the operation;
8. Patient has a known diagnosis of defective hemostasis and past history of clinical bleeding requiring transfusion and treatment;
9. Patient has had an operative procedure involving the eye, ear, or central nervous system within one month;
10. Patient has severe uncontrolled hypertension with systolic BP > 220mmHg or diastolic BP > 120mmHg;
11. Patient has an absolute body weight of less than 41 kilograms (90.4 lbs) at baseline visit; or
12. The patient is in a vulnerable patient population (ie. prisoners and institutionalized individuals).

If women of child-bearing potential do not already have a urine pregnancy test on the morning of surgery as part of their clinical care, one will be done prior to receiving any study medication. Women of child bearing potential include women who are premenopausal who have not had a bilateral oophorectomy, hysterectomy or tubal ligation. A woman is considered post-menopausal when she has not had a menstrual period for at least one calendar year. Women who have a positive urine pregnancy test on the morning of surgery will be considered a screen fail and will not be eligible to participate in the trial.

### Enrollment Procedures

There will likely be several opportunities for recruitment contact with potential patient study enrollees. As an example, the MUSC format is provided below as a template that can be adopted or modified as appropriate:

1. Initial discussion and introduction to the study will occur with the treating surgeon in the ambulatory office setting at the time of patient decision to pursue elective THA or TKA, primary or revision, accompanied by the PEPPER informational brochure. The operating surgeon will uniformly endorse participation of all patients in the study;
2. The surgery scheduler in surgeon’s office will contact the patient to confirm the surgical date and enters contact information into the Pre-Screening Form. Once the coordinator determines patient eligibility for screening, the scheduler mails educational materials for the PEPPER trial to the patient, including detailed study information and consent documents;
3. After receipt of informational materials by the patient, the PEPPER site coordinator initiates contact with the patient by telephone to further discuss the trial, review consent, and solicit participation and enrollment;
4. At the time of the preoperative visit for surgical clearance, the PEPPER site coordinator and/or surgeon meets with potential patient participants in person to review the trial and, ideally, obtain informed consent and signed documents. At this time the Hip (or Knee, as appropriate) Baseline Survey will be completed. If the patient remains uncertain about participation, the site coordinator and/or surgeon will respond to any remaining questions from the patient and contact the patient by phone in follow-up to this visit to further develop understanding and confidence of the patient to participate in the trial; and
5. The final opportunity to obtain consent will occur at any time up to, and including, one day before surgery. If the patient agrees, the coordinator and patient will arrange a time to authorize consent and complete the baseline instruments. Consent obtained at this time will, by definition, have been preceded by several conversations between the study coordinator and/or surgeon and the patient to ensure the informed nature of the consent.

*Written consent on the telephone*

Effective 7/18/17, if a patient is unable to sign the consent form during a pre-operative clinic visit, or wants more time to consider participation in the trial and is unable to return to clinic to sign the form prior to surgery, written consent may be obtained via telephone. Obtaining written consent over the phone may only be done after the study has been introduced to the patient via a face to face meeting. The patient will sign their copy of the consent form while the coordinator signs one as well. The patient will either mail or fax their copy to the coordinator who will merge the two copies to form one fully executed consent form. Once the form has been received by the coordinator, the patient can complete the baseline assessments. Baseline assessments must not be completed until the signed copy of the consent form has been received from the patient and co-signed by the coordinator. For those sites that are required to have a separate consent and HIPAA authorization, the HIPAA authorization must also be signed, dated, and sent in via mail or fax in order to begin study procedures.

At any point prior to surgery, should the prospective study patient have any questions regarding the procedures of the study, the coordinator and/or the surgeon will answer all questions to the patient’s satisfaction.

Consent to participate in the study may be obtained by the study site coordinator or any other appropriately qualified and approved study staff member. Upon obtaining informed consent, each site coordinator will collect baseline information from the patient concerning comorbidities, joint function, and general well-being data using the respective hip or knee disability and osteoarthritis outcomes scores (HOOS and KOOS), the Oswestry and Charlson instruments, and the PROMIS-10 global health survey. Baseline instruments should be collected within 3 months of the patient’s operation. These data should be entered into the [PEPPER EDC](https://app.gsrweb.com/musc/) database and the completed paper form kept in the study participant file.

Following informed consent, the surgeon will sign off on all eligibility criteria using the Screening Surgeon Screening Sign Off form and the patient will be considered enrolled and eligible for randomization. Also following consent, patient contact information is collected on the Patient Contact Form and entered into the EDC system.

### Randomization

A centralized randomization schedule will provide assignment to one of the three prophylaxis regimens (aspirin, warfarin, or rivaroxaban) in randomly varying block sizes developed separately for each clinical site and stratified according to type of surgery (hip or knee replacement).

Randomization of consented patients will occur no earlier than 10 days and up until 1 day before the scheduled surgery date. Effective 7/18/17 (Amendment 12), it is no longer considered a protocol deviation if, as a consequence of a patient’s surgery being rescheduled, their randomization falls outside the 10 day window. If a patient’s surgery is postponed, or cancelled and ultimately rescheduled, the patient will keep the original randomization assignment. The ability to randomize a patient will be available via the web-based randomization system once consent has been signed and all baseline instruments have been entered into the database. Study group assignments will be shared with the surgeon at the time of randomization, and with the patient on the day of operation unless necessary to provide third party insurance coverage for prescribed medical care.

In the absence of any randomization stratification limitations, patients meeting all eligibility criteria without any randomization exclusions will be assigned to one of three groups. Prophylaxis will continue for 30 days, in accordance with clinical guidelines:

1. enteric coated aspirin (regimen with lowest bleeding risk; clinical PE and all-cause mortality rates comparable to more intensive anticoagulants);
2. low intensity warfarin (target INR 1.7-2.2) (time honored and one of the most common North American regimens; low bleeding risk [1-2%]); and
3. rivaroxaban, an oral direct Factor Xa inhibitor (regimen with lowest PE and DVT rate but higher bleeding risk [3-5%]).

A contraindication to one of the three study prophylaxis regimens for venous thromboembolism will result in stratified randomization and a corresponding stratified analysis.

Randomization will be stratified and restricted to assignment to either warfarin or rivaroxaban as follows:

1. Patients with a known aspirin allergy;
2. Patients with a personal history of PE or DVT;
3. Patients with a known condition of thrombophilia proven by diagnostic testing; e.g. Factor V Leiden; or
4. Patients wth a diagnosis of cancer who are under active treatment.

Randomization will be stratified and restricted to assignment to either aspirin or warfarin as follows:

1. Patients with a serum creatinine greater than 2.0 mg/dl; or
2. Patients taking medications that interfere with metabolism of rivaroxaban via CYP 3A4 inhibition (most commonly protease inhibitors used in treatment of HIV)[[1]](#footnote-1).

Randomization will be stratified and restricted to assignment to either aspirin or rivaroxaban as follows:

1. Patients with a history of necrotizing skin lesions related to warfarin therapy.

If after randomization a participant is unable to take the assigned medication due to financial constraints, or new information becomes available that affects the safety of the participant, the surgeon will use his/her discretion in assigning the patient to one of the other arms of the trial. This change is effective 7/18/17 and no longer warrants submission of a protocol deviation (Amendment 12). However, attempts should be made to seek assistance, for example, through use of the 340B federal drug pricing program. (see

Participants must be withdrawn from the study if they do not receive one of the three medications at the same dosage level being studied in the trial. If a patient received a medication other than one of the three PEPPER approved treatment groups and remains on this medication, the patient should be withdrawn from the study regardless of their willingness to be followed.

## Description of Study Intervention

Administration of study medications will occur in accordance with current standard of care practice and commence on the morning of surgery for the aspirin and warfarin groups, and 24 hours after the completion of surgery for the rivaroxaban group. Drug treatment in all three study groups will continue through 30 days after operation. Aspirin and rivaroxaban dosing during this time is pre-specified and empirical. Warfarin dosing will be adjusted to a target INR of 2.0 according to the standard monitoring practice of the local site, typically by blood draw twice weekly to check the INR and adjust warfarin dosing accordingly. In the event of the occurrence of any primary study VTE outcomes or adverse events, study medication administration will cease and subsequent management will be according to standard medical treatment and best clinical judgment of the treating physician/surgeon. Data collection on each of these patients will continue through to complete follow-up of 6 months as for all study patients. At the time of discharge, each patient will be provided with instructions and/or a prescription for the assigned anticoagulant to complete 30 days of post-operative prophylaxis per study protocol and standard practice.

Patients on chronic (more than 6 months) warfarin or rivaroxaban therapy will be excluded from participation in the PEPPER trial. Patients on cardiac dose aspirin may participate in the trial and will either continue their regular cardiac dose aspirin if randomized to warfarin or rivaroxaban groups, or change their aspirin dosing to conform with that of the PEPPER trial if randomized to the aspirin treatment group.

Participants will be randomized according to the algorithm described above, and begin receipt of the assigned medication on the day of surgery according to one of the following regimens:

***Aspirin group*:** Enteric coated aspirin (162 mg po) will be administered on the day of operation, prior to surgery, with a sip of water. Thereafter, starting on postoperative day #1, all patients in the aspirin group will receive 81 mg po bid to complete the treatment period of 30 days. Patients on preoperative cardiac dose aspirin may continue their usual dosing regimen prior to the morning of surgery, and then commence the PEPPER trial aspirin dose of 81 mg po bid on the day after operation.

***Warfarin group*:** Warfarin will be administered starting on the day of operation, prior to surgery, with a sip of water. The initial dose will be empirically determined by body weight: less than 125 lbs (56.7 kg) – 2.5 mg; 125-250 lbs (56.7-113.4 kg) – 5 mg; greater than 250 lbs (113.4 kg) – 7.5mg. The initial dose will be repeated on the evening of surgery if the preoperative dose was administered prior to noon on the day of operation; no warfarin will be given on the evening of surgery if the preoperative dose was received after noon on the day of operation. Thereafter, starting on postoperative day #1, warfarin will be given each evening based on INR values to achieve a target of 2.0 (range 1.7-2.2).

***Rivaroxaban group*:** Rivaroxaban 10 mg will be first administered approximately 24 hours after completion of surgery. Medication will then be administered in the evening on postoperative day #2 and thereafter each evening until completion.

### Schedule of Events

*Prior to Baseline:*

Completion of Pre-Screening and Patient Recruitment forms.

*No more than 3 months prior to the day before surgery:*

Comletion of Screening and Surgeon Sign Off form, Patient Contact Form, written Informed Consent, completion of baseline instruments (HOOS/KOOS, Oswestry Instrument, Charlson Comorbidity Index, PROMIS-10)

*No more than 10 days to 1 day before surgery:*

Completion of the Randomization form to document any contraindications to the medications and record the treatment assignment resulting from randomization in the EDC system. Adverse events monitoring begins.

*Surgery:*

Study drug administration (aspirin or warfarin) begins and continues for 30 days.

*Post-Operative day 1:*

Study drug administration (rivaroxaban) begins and continues for 30 days. Confirmation of surgery entered into EDC.

See [Appendix D. Schedule of Events](#_Appendix_D:_Schedule) for detailed information in tabular format.

### Peri-Operative Data Collection

The Surgical Adherence Form must be completed and entered into the EDC system within two business days of surgery. The receipt of this data prompts two processes: 1. The timing of subsequently follow-up windows, within which the 1-month, 3-month, and 6-month follow-up surveys will be administered; and 2. designation of the patient as “reimbursable” for the purposes of invoicing and reimbursement by the CCC.

The Surgery Data Form must be completed and entered into the EDC system withintwo business days of the patient being discharged from hospital.

### Follow-up Windows

Study patients will be contacted at 4 weeks (+ 10 days), 3 months (+/- 10 days), and 6 months (+/- 4 weeks) after surgery by Statix, LLC to collect patient-reported outcomes data. Up to ten attempts will be made by Statix to obtain follow-up of research subjects through mail, telephone, electronic communication, and web-enabled online surveys. Central PRO data collection personnel will interrogate for comorbidities, joint function, and general well-being information using either the hip or knee disability and osteoarthritis outcome scores (HOOS and KOOS, respectively) as well as the PROMIS-10 global health survey. In the event that a patient has not been reached to complete the follow-up assessments, the study coordinator will contact the patient or present to the follow up clinic visit to facilitate completion of the surveys with the patient. Any adverse events reported to Statix personnel in the course of collecting follow-up data from the patient and/or *ad hoc* event discovery by site coordinators will prompt a process of event recording and adjudication by the OAC (see [8 Safety Assessment and Reporting](#_SAFETY_ASSESSMENT_AND) for additional information).

Final medical record review will be performed by the on-site coordinators on all participants who experience either endpoint events or adverse events, and those who fail to otherwise respond to follow-up data collection efforts. Final medical record review will occur 6 months after surgery, or at completion of study follow-up, whichever comes first. This final site coordinator medical record review will capture events missed by interview from patient failure to report for follow-up or respond to calls.

### Outcome Determination

Only important ***clinical endpoints and functional outcomes that matter to patients*** will be assessed. The primary effectiveness outcome (benefits) will be the aggregate of all-cause mortality and clinical PE and DVT, confirmed by imaging and resulting in readmission. *Deaths* will be classified either as cardiovascular, if sudden and otherwise unexplained, or caused by myocardial infarction, stroke, arrhythmia, heart failure, pulmonary embolism, or other cardiovascular event. For patients with more than one clinical event, only the first or most serious event will be counted. *Primary safety endpoints* (harms) include major bleeding, clinically important wound and remote bleeding, persistent wound drainage, reoperation for treatment of the wound or removal of the implant for infection, myocardial infarction, and patient-reported function at 4 weeks, 3 months, and 6 months after operation. *Major bleeding* is defined as that which is fatal, occurs in a critical organ or space (retroperitoneal, intracranial, epidural, intraspinal, intraocular, pericardial), results in reoperation, or remote site bleeding that is clinically overt (blood or its breakdown products seen in volume and clinically evident as a collection or mass) and associated with a fall in hemoglobin of at least 2 g/dL, managed with transfusion of two or more units of red blood cells, or prolongs the hospital stay. *Non-major clinically important wound-related bleeding* is defined as persistent drainage beyond 5 days after operation; this increases risk of deep infection and threatens long-term device function. There will be no screening for VTE; diagnostic testing will be performed only for clinical indications. DVT will be diagnosed by loss of compressibility on venous ultrasound or evidence of a filling defect on invasive contrast venography. PE will be diagnosed on the basis of contrast-enhanced chest computed tomography, ventilation-perfusion lung scanning, or pulmonary angiography. Myocardial infarction will be diagnosed by laboratory-defined elevation in troponin and/or appropriate changes on electrocardiogram. *Suspected VTE-related clinical events will not be counted unless confirmed by diagnostic imaging.* Audit of pertinent events will occur at the time of enrollment in the study, at hospital discharge, and 4 weeks, 3 months, and 6 months after operation. All endpoints will be adjudicated by investigators (OAC) who are unaware of patient group assignments.

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# SAFETY ASSESSMENT AND REPORTING



## Definition and Reporting of Serious Adverse Events

### Definition

Serious adverse events (SAE) will be defined as any death or unplanned readmission to the hospital, reoperation or other procedure related to the index operated joint, transfusion, aspiration of the operated joint, or any other event that may be attributed to use of one of the anticoagulant medications central to the clinical trial. Event-related supporting documentation will be provided to the CCC and OAC by the clinical sites in accordance with guildelines provided in section [8.2](#_Outcomes_Assessment_Committee) of this MOP. Events will be adjudicated by the OAC and considered by the DSMB in their regular reviews; they will be reported to the IRB as appropriate and determined by the DSMB and executive oversight group.

### Expectedness

Adverse events may be expected or unexpected. If an event is generally recognized to be a risk associated with the intervention then the event is considered expected. Expected risks in this trial include any and all of those typically experienced in the course of “standard of care” treatment and prophylaxis for venous thromboembolism after total hip or knee replacement. These include a risk of bleeding, reoperation to evacuate a hematoma from the incision, secondary infection of the hematoma, deep venous thrombosis, and pulmonary embolism (Table 1). Aspirin may cause gastritis and intestinal bleeding may result, or patients may develop an allergy to aspirin that interferes with breathing. Warfarin may accumulate in patients who have liver disease or result in an idiosyncratic reaction with elevation of the INR and may require reversal. Rivaroxaban may accumulate in patients who have kidney disease and may require reversal or other treatment as appropriate. Events outside of the recognized risks associated with knee or hip replacement or revision, or any of the medications used for prophylaxis of thromboembolism will be considered unexpected.

Table 1. Estimated risks associated with re-operation for bleeding and pulmonary  
embolism

|  |  |  |
| --- | --- | --- |
|  | **Risks** | |
| **Medication** | **Reoperation for Bleeding** | **Pulmonary Embolism** |
| Aspirin | 1 in 500 (0.2%) | 1 in 50 (2.0%) |
| Warfarin | 1 in 100 (1.0%) | 1 in 100 (1.0%) |
| Rivaroxaban | 1 in 20 (5.0%) | 1 in 200 (0.5%) |

### Causality

In adjudicating specific adverse events, the OAC will assess the relationship or association of the study medication in causing or contributing to the adverse event. Events will be characterized using the following classification and definitions:

* *Unlikely:* The adverse event, at the time it is evaluated, is judged to be unlikely related to the study medication.
* *Possibly:* A causal association of the adverse event with the study medication may exist based on the temporal sequence of the event in relation to administration of study medication or the known response pattern to the study medication. However, the event can be explained by other causes.
* *Probably:* A causal association of the adverse event with the study medication seems likely based on the temporal sequence of the event in relationship to administration of study medication, the known response pattern to the study medication, or judgment based on the investigator’s clinical experience. However, other causes cannot be ruled out.
* *Definite:* A definite causal relationship exists between treatment with the study medication and the adverse event based on the temporal sequence of the event in relationship to the administration of study medication, the known pharmacological action of the study medication, and known adverse reactions to the study medication or medications of the same class. In addition, the event cannot be explained by other causes.

### Severity

The severity of the adverse event will be rated as mild, moderate, or severe using the following

criteria:

* *Mild:* The adverse event is noticeable by the participant or observer, but causes minimal discomfort or concern, may require minimal or no treatment, and does not interfere with the participant’s daily activities.
* *Moderate:* The adverse event results in a low level of discomfort, inconvenience or concern for the participant, and may interfere somewhat with normal functioning or daily activities, but is usually ameliorated by simple therapeutic measures.
* *Severe:* The adverse event causes significant discomfort or incapacitation and may require prescription drug therapy, other treatments or interventions.

## Outcomes Assessment Committee

Events will be identified by Statix staff while conducting follow-up data collection (at approximately 1 month, 3 months, and 6 months after surgery), or by site coordinators on an *ad hoc* basis when they become aware of an adverse event, *or* if they are required to complete follow-ups when Statix is unable to contact participants. A positive response to any one of the questions on the first page of the follow-up survey will trigger the Statix database to “flag” a patient’s record. An analogous form exists for site coordinators’ use (Adverse Event Reporting form). The flagged record will be identified and reported both to the CCC and the appropriate clinical site in the weekly report provided by Statix immediately following the event identification. The site coordinator will then be responsible for gathering a specified list of clinical records relating to the event (as listed on the Adverse Event Supporting Documentation form) and uploading the data to the [EDC system](https://app.gsrweb.com/musc/). This may involve obtaining medical records from an outlying facility where the patient was treated. These documents must be redacted of all PHI *except* the date of the event, including any reference to the randomization assignment. Any documents transferred to the CCC outside of the EDC system must be sent via secure email. The CCC will download and organize the documents and forward to the Outcomes Assessment Committee (“OAC”) for review and adjudication. The OAC will provide their analysis to the DCC and CCC, for delivery to the DSMB for review, assessment, and report.

Copies of the joint-specific follow-up surveys, Adverse Event Reporting form and Adverse Event Supporting Documentation form are available for download from the [PEPPER website](http://www.muschealth.org/pepper/index.html).

## Event Adjudication Workflow

**OAC**

**Clinical Site**

*Ad-hoc coordinator discovery*

**Statix**

*PROs 1, 3, 6m  
follow-up*

**CCC**

Triage

Organize, collate records

Data entry

**IRB**

Chair review

Reviewer #1  
Reviewer #2

## Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is appointed by the PI and PCORI leadership and comprises five expert investigators in disciplines relevant to the study, including orthopaedic surgery, biostatistics and large clinical trials epidemiology, patient-centered outcomes research, and thrombosis and hemostasis (hematology).

DSMB members will serve in an advisory capacity and report to the Steering Committee (SC) and Executive Oversight Committee (EOC). They will monitor accruing data to assure that patients in the clinical trial are being cared for safely. The DSMB will be responsible for:

* Review of the research protocol, informed consent document, and plans for data and safety monitoring;
* Advising study leadership as to the readiness of the study staff to initiate recruitment;
* Considering factors external to the study when relevant new information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
* Reviewing and analyzing the progress of the clinical trial;
* Approving amendments to the clinical trial protocol if warranted;
* Ensuring the confidentiality of the study data and the results of monitoring;
* Monitoring the safety of study treatments;
* Protecting the safety of study participants;
* Reviewing data quality;
* Reviewing interim analyses and recommending early termination or continuation of the trial; and
* Assisting PCORI and study leadership by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

Confidentiality will be maintained during all phases of DSMB review and deliberations, and participants in DSMB meetings will maintain strict confidentiality concerning all privileged trial results provided to them. Only results for the entire study population (without regard to treatment group) will be presented during open sessions of the DSMB. Presentation of patient-specific information (eg. SAE reports) will not include information that would allow the identification of individual participants. Treatment group-specific data presented in closed session reports will be labeled Group A, B, or C in case the documents are inadvertently viewed by individuals other than those participating in the closed session. However, at the meeting, DSMB members will be informed of the identity of the groups (aspirin vs. warfarin vs. rivaroxaban) only and as necessary to make determinations of alteration or discontinuation of study groups as necessitated by disparate event rates. Both Board members and others invited to participate in DSMB meetings are expected to maintain confidentiality.

The PI with the DCC will provide regular reports to the DSMB and additional information as requested. The DSMB may convene in face-to-face meetings or on conference calls and will discharge itself from its duties when the study is complete. Study completion will be considered in consultation with the PI and PCORI after no further outcome data are being collected, data analysis is complete, and the main paper reporting on the primary outcomes has been published.

The DSMB will review study data reports every six months. Data safety monitoring is based on narrative summaries of each serious or unexpected adverse event (SAE) organized through the OAC. On a monthly basis, a tabular summary of SAEs and their classification status will be provided to the DSMB. Every six months the DSMB and PCORI will receive a report on the clinical trial, presenting S/AEs in tabular form as well as outcome information to evaluate safety for the purposes of approving or disapproving continuation of the clinical trial. SAEs will be considered by the DSMB in their regular reviews and reported to the IRB as appropriate and determined by the DSMB and executive oversight group. DSMB reports will be provided to the IRB as appropriate and per institutional policy.

# DATA MANAGEMENT



## Data Management

At monthly intervals Statix will transfer form files electronically to Axio and the Data Coordinating Center (DCC) at the University of Maryland. The DCCenter will archive those form files, edit them for completeness of forms and data items, edit them for within-form and across-form logical consistency of data items, and report on the edits to the Clinical Coordinating Center (CCC). Statix will work with the DCC and the CCC to achieve complete form submission and correct errors in data items submitted.  Delinquent forms and data item corrections will be submitted through the DCC in a process of continual form file updating. The DCC will work with Axio to convert the form files into data analysis files, and the study biostatistician will analyze those data files in consultation with the DCC leadership and PI for preparation of reports to the Data and Safety Monitoring Board (DSMB) every six months.

There will be no outcome or endpoint data exchange between clinical sites other than the sharing of enrollment figures and progress towards enrollment goals at each site. This information will be made available in a secure section of the clinical trial website that is password protected and available only to clinical sites and their staff.

Refer to the PEPPER Protocol for information about the Analysis Plan.

## Maintaining Data Privacy

Clinical sites should follow local requirements for maintaining confidential participant records.

At a minimum:

* Any and all paper records relating to patients screened for PEPPER and participants enrolled and followed in PEPPER will be kept in locked cabinets in a secure location;
* Any paper records requiring destruction will be shredded either in the presence of the staff person or by a certified document destruction contractor;
* All medical records extracted for the purposes of supplementing SAE reports to the OAC will be identified only by the participant ID;
* A waiver of consent will be obtained to screen participants for PEPPER in order to collect certain elements of PHI prior to obtaining signed informed consent from the participant;
* The Participant Screening Log will be password-protected and encrypted with the password adhering to password strength requirements described below;
* Email and other communication with the CCC/DCC will refer to participants by their participant ID ONLY. PHI will be removed/obscured from any documents or files forwarded to the CCC/DCC.
* Any computers, laptops, tablets or other devices used to track or enter information relating to PEPPER participants will be protected as follows:
  + Access to the device will require individually assigned user ID/password;
  + The password must be a minimum of 8 characters in length and contain at least 3 of the following character types: lower case letters, upper case letters, digits, special characters;
  + A screensaver must be activated requiring entry of a password to re-activate after no more than 15 minutes of inactivity; that password must adhere to the above rules for password strength;
  + Connection to the internet must be via hard-wire or secure, encrypted wireless network;
  + A firewall must separate the device from the internet;
  + The device must have currently updated virus software installed and running;
  + Any files residing on this device or on a file server containing PHI related to PEPPER participants will be separately password protected and encrypted; and
  + No files containing PHI related to PEPPER participants may be stored on an external device (eg. USB flash drive).

If files containing PHI for PEPPER participants are saved to a file server, the directories on that file server must be secure so that only personnel involved with PEPPER and listed on the site delegation log have access to those directories.

## Reporting Plan

Publication and communication of findings will be made in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and its extension for pragmatic clinical trials. In addition to following the standard CONSORT guidelines, reports will detail information about the characteristics of the study population and clinical centers so that providers and patients will have a good idea of the degree to which findings can be generalized to their own populations. This will include information regarding clinical centers chosen, number of patients invited to participate, number participating, age and clinical conditions of patients (including comorbidities), patient adherence, and clinical management of patients beyond what is prescribed by treatment regimens (proportion receiving hip vs. knee operation types, anesthesia types, etc).

## Data Sharing

Proposed dissemination activities are designed to achieve two objectives: (1) increasing uptake of findings of the study; and (2) integration of the shared decision on anticoagulation choice into routine care.

The presentation of study findings at scientific meetings, and in scholarly publications, will target different clinical populations: orthopaedic surgeons, anticoagulation specialists, and hospitalists/general internists. Working with the Patient Advisory Board and the MUSC marketing department, we will create a dedicated PCORI PEPPER trial MUSC website to serve as a resource for patients and study sites, as well as materials that advisory board members can post on patient advocacy organization websites. To reach health professionals that do not routinely review the medical literature, we will create short descriptions of the study results for posting on the websites of participating institutions, and on Medscape and Doximity medical social networks. Finally, to reach interested patient constituents, we will rely upon the networking reach of patient advocacy groups represented on the Steering Committee, as well as promotional support from AARP at the conclusion of the trial when event rates will be available for each treamtent group and related subgroups of patients.

With regard to activity (2), we will perform additional analyses designed to help surgeons, physicians, and other medical providers apply the results to individual patients. We will examine associations between demographic factors and conjoint analysis studies, and describe this in publications where appropriate to help physicians tailor interpretations of the study. We will examine risks in subgroups to assess the degree to which non-inferiority of treatments extends to patients with different levels of risk factors (chronic illness, prior vascular disease, smoking, etc.) in order to provide guidance for tailoring stakeholder choice of intervention and balancing benefits and harms for specific individuals. Our purpose is not to assign causality but to develop models that, when exposed via the study website, can help providers and patients determine when there is truly non-inferiority. We will also adapt our preference elicitation tools into web friendly formats, coupled with explanations of the meaning elicitations, to help surgeons better understand what their patient values are and post these tools on publically accessible web sites. In addition we will create a web site describing the results of the study, from a patient perspective based on input from our patient advisory board, that can serve as a prototype for subsequent developers of decision aids. Finally, pragmatic dissemination of shared decision making modules will occur directly to patients through the EPIC MyChart portal.

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# SITE MONITORING PLAN



## Site Communication

Conference calls, e-mails, and telephone calls will be used to maintain frequent and regular communication between the Clinical Coordinating Center (CCC) and the clinical sites. Questions and concerns raised by sites about the protocol or operationalization will be used to collate a “Q&A” guide for coordinators’ reference. The CCC will initiate contact with any sites who are not in periodic contact for protocol or other reasons to enquire about their status; we anticipate these sites will have solved common problems effectively and will be able to share information that may help other sites. This information will be compiled in a Best Practices Guide for PEPPER coordinators. Both the Clinical Operations Q&A and Best Practices Guide will be made available on the [PEPPER website](http://www.muschealth.org/pepper/index.html) and updated regularly.

## Enrollment Tracking

The CCC will develop an “Enrollment Tracking Tool” to monitor both site and overall study enrollment-related metrics during the period of data collection. These tools will monitor overall site performance, including the number of patients screened, consented, and enrolled. Both absolute enrollment and the enrollment rate will be measured on a per month, and cumulative basis. Site and overall study progress towards enrollment goal achievement will also be estimated. Graphical representations of month-by-month and cumulative enrollment will assist with the identification of trends. Site-specific aggregate absolute and cumulative enrollment will be posted on the [PEPPER website](http://www.muschealth.org/pepper/index.html) for site investigators and coordinators to review their relative success in reaching enrollment goals in comparison to other sites.

## Site Visits

Site visits will be undertaken for two reasons. Firstly, the PI and one other member of leadership (this may be the National Program Manager (NPM), a member of the Executive Oversight Committee (EOC), or a member of the Steering Committee (SC)) will attempt to visit all clinical sites at least once during the three-year data collection period to discuss the progress of the study with the site PI and coordinator(s), and learn from the site’s experience conducting the study.

In the event a clinical site is unable to maintain its monthly enrollment goal, the CCC will initiate contact and attempt to identify and problem-solve the barrier(s) to enrollment so that supportive and remedial action can be taken. This initial contact will be made by CCC staff directly to the site coordinator(s), and an appropriate period of time will be observed to establish if any adopted strategies have been successful. If there is no evidence of improvement after a specified length of time, the study PI along with the NPManager and/or another member of the CCC will schedule a conference call with the PI and coordinator at the clinical site to discuss further strategies to remove barriers and increase site enrollments. A site visit visit by the PI and/or other member(s) of leadership may be required if a site requires additional asistance to accelerate their progress towards goals. As a last resort, and if it becomes evident that the site is unwilling or unable to improve its performance to acceptable levels, the decision may be made to retire the site from the study.

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# STUDY COMPLETION AND CLOSEOUT PROCEDURES



## Site Close-out Procedures

Before the PEPPER study can be considered closed, necessary steps must be completed to ensure all aspects of study have been addressed. The PI, CCC, DCC, and Clinical Sites each have specific items to be completed; these are provided in more detail in [Appendix E: Study Close-Out Checklist](#_Appendix_E:_Study).

## Data Locking Procedures

Statix will remove identifiers and contact information from the complete dataset of participant clinical and PROs data and send this to the PI for permanent secure storage; the data housed by Statix will be permanently purged.

## Final Study Report

The final study report will be submitted to PCORI according to PCORI guidelines.

## Long Term Storage of Study Documentation

Study records and documents including CRFs, source documents, consent forms, and any other study-related financial or administrative documents must be retained by the investigator for a period of three years from the a) PCORI contract term date, b) date of the final payment under this contract, or c)

conclusion of any audit or litigation related to this contract, whichever is later, *or* as required by institutional standards, whichever is the longer.

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# APPENDICES



## Appendix A: 340B Federal Drug Pricing Program

The 340B Drug Pricing Program is a federal initiative administered by the Health Resources and Services Administration (HRSA) to assist healthcare entities (covered under Section 340B(a)(4) of the Public Health Service Act) serving a disproportinate number of un- or under-insured patients offer medications to their patients at discounted prices.

Few patients randomized to rivaroxaban are faced with unaffordable copays. Nevertheless, there is a subset of patients – who appear to predominantly be on Medicare Part D – for whom rivaroxaban is not covered and who face copays in the $200-$300 range.

At MUSC, the protocol for identifying – and offering assistance – to individuals facing large copays when randomized to rivaroxaban is as follows:

1. The PEPPER team randomizes all study participants on the Wednesday before their qualifying surgery. This ensures that all surgeons, residents, and associated clinicians are made aware of study participation and assigned anticoagulants during their Total Joint Conference on Thursday mornings (when upcoming surgeries are reviewed and discussed);
2. Assignments are also sent to the pharmacy, where test claims are run for all patients randomized to rivaroxaban;
3. If a test claim returns a cost of >$50, the pharmacist contacts the patient to confirm the copay is aceptable. If this is unsuccessful, the pharmacy will utilize the 340B program in an attempt to reduce the copay to an affordable amount (currently approximately $70[[2]](#footnote-2)).
4. If the patient is still unwilling/unable to pay for the rivaroxaban, s/he may be reassigned to another of the study medications (at the surgeon’s discretion), which should be prescribed and administered per protocol.

Additional information about the program, including educational resources, eligibility, program requirements, and a database of all 340B-certified entities in the US can be found at https://www.hrsa.gov/opa/.

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## Appendix B: List of Abbreviations

|  |  |
| --- | --- |
| CCC | Clinical Coordinating Center |
| Co-I | Co-Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| DCC | Data Coordinating Center |
| DSMB | Data and Safety Monitoring Board |
| DVT | Deep vein thrombosis |
| EDC | Electronic Data Capture |
| eIRB | Electronic Institutional Review Board |
| EOC | Executive Oversight Committee |
| HIPAA | Health Insurance Portability and Accountability Act |
| HOOS | Hip Disability and Osteoarthritis Outcome Score |
| ICF | Informed Consent Document |
| IRB | Institutional Review Board |
| KOOS | Knee Injury and Osteoarthritis Outcome Score |
| MOP | Manual of Procedures |
| MUSC | Medical University of South Carolina |
| NPM | National Program Manager |
| OAC | Outcomes Assessment Committee |
| PAB | Patient Advisory Board |
| PCORI | Patient Centered Outcomes Research Institute |
| PE | Pulmonary embolism |
| PEPPER | Pulmonary Embolism Prevention after HiP and KneE Replacement: Balancing Safety and Effectiveness |
| PI | Principal Investigator |
| PRO | Patient Reported Outcomes |
| PROMIS | Patient Reported Outcomes Measurement Information System |
| VTE | Venous thromboembolism |

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## Appendix C: Cumulative Target Enrollment

|  |  |
| --- | --- |
| **Month** | **Cumulative Target Enrollment** |
| 1 | 695 |
| 2 | 1,390 |
| 3 | 2,085 |
| 4 | 2,780 |
| 5 | 3,475 |
| 6 | 4,170 |
| 7 | 4,865 |
| 8 | 5,560 |
| **9 (25%)** | **6,255** |
| 10 | 6,950 |
| 11 | 7,645 |
| 12 | 8,340 |
| 13 | 9,035 |
| 14 | 9,730 |
| 15 | 10,425 |
| 16 | 11,120 |
| 17 | 11,815 |
| **18 (50%)** | **12,510** |
| 19 | 13,205 |
| 20 | 13,900 |
| 21 | 14,595 |
| 22 | 15,290 |
| 23 | 15,985 |
| 24 | 16,680 |
| 25 | 17,375 |
| 26 | 18,070 |
| **27 (75%)** | **18,765** |
| 28 | 19,460 |
| 29 | 20,155 |
| 30 | 20,850 |
| 31 | 21,545 |
| 32 | 22,240 |
| 33 | 22,935 |
| 34 | 23,630 |
| 35 | 24,325 |
| **36 (100%)** | **25,020** |

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## Appendix D: Project Timeline and Deliverables

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PROJECT TIMELINE and DELIVERABLES (\*)** | Year: | Year 1 | | | | | | | | | | | | Year 2 | | | | | | | | | | | | Year 3 | | | | | | | | | | | | Year 4 | | | | | | | | | | | | Year 5 | | | | | | | | | | | |
| 3/1/2016–9/1/2020 Quarter: | | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | | 6 | | | 7 | | | 8 | | | 9 | | | 10 | | | 11 | | | 12 | | | 13 | | | 14 | | | 15 | | | 16 | | | 17 | | | 18 | | | 19 | | | 20 | | |
| \*Task 1: Develop/refine patient preference Q-aires | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 2: Develop Final Policy/Procedure Manual | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 3: Consent develop/MUSC central IRB | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 4: Registration at ClinicalTrials.gov | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 5: Ongoing Patient Enrollment | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 6: Ongoing Patient Randomization | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 7: Rolling monthly enrollment reports | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 8: Rolling patient outcome data reports | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 9: Site prep/all local IRBs complete, enroll | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 10: Patient Advisory Board (PAB) Review | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 11: Outcomes Assessment Com (OAC) Review | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 12: Data & Safety Monitoring Board (DSMB) | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 13: Semi-annual interim data analysis | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 14: Steering Committee Monthly Conf Call | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 15: Enrollment target – 25% | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 16: Enrollment target – 50% | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 17: Enrollment target – 75% | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 18: Enrollment closure – 25,000 patients | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Task 19: Final follow-up patient data collection | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 20: PAB event/patient preference analysis | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 21: Final data analysis and review | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 22: Information dissemination, final report | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 23: Manuscripts: 1o/2o outcomes; PROs; Pt pref | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*Task 24: De-identified data sharing: 54-63 mos | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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## Appendix E: Schedule of Events

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Screening** | **Baseline  (-3 months to -1 day)** | **Randomization  (-10 days to -1 day)** | **Surgery  (Day 0)** | **Post Op (Day 1)** | **Hospital Discharge** | **4 Week FU  (+ 10 days)** | **3 Month FU  (+/- 10 days)** | **6 Month FU  (+/- 1 month)** |
| Pre-Screen Form | X |  |  |  |  |  |  |  |  |
| Screening Form | X |  |  |  |  |  |  |  |  |
| Eligibility Review | X |  |  |  |  |  |  |  |  |
| Written Informed Consent |  | X |  |  |  |  |  |  |  |
| HOOS/KOOS |  | X |  |  |  |  | X | X | X |
| Oswestry Instrument |  | X |  |  |  |  |  |  |  |
| Charlson Comorbidity Index |  | X |  |  |  |  |  |  |  |
| PROMIS-10 Global Health Survey |  | X |  |  |  |  | X | X | X |
| Randomization |  |  | X |  |  |  |  |  |  |
| Urine pregnancy test |  |  |  | X1 |  |  |  |  |  |
| Study Drug Administration (Aspirin and Warfarin Arms) |  |  |  | X  (ongoing for 30 days) | X | X | X |  |  |
| Study Drug Administration (Rivaroxaban Arm) |  |  |  |  | X  (ongoing for 30 days) | X | X |  |  |
| Perioperative Form |  |  |  |  |  | X |  |  |  |
| AE/SAE Monitoring |  |  | X | X | X | X | X | X | X |

1 Urine pregnancy test done as part of the patient’s standard of care; the results will be reviewed for research purpose.

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## Appendix F: Study Close-out Checklist

| ***No.*** | ***Task*** | ***Owner*** | ***Date Completed*** | ***Comments*** |
| --- | --- | --- | --- | --- |
| ***Form/log completion (\*Will be captured electronically only)***  Confirm that all necessary CRFs have been completed, collected, and the proper legible copies are present in participant files. Include patients who were screened but not eligible, eligible but not enrolled, and all enrolled participants. | | | | |
| 1 | Patient Contact Form | Clinical sites |  |  |
| 2 | Pre-Screen | Clinical sites |  |  |
| 3 | Randomization | Clinical sites |  |  |
| 4 | Baseline Form (both Hip and Knee) | Clinical sites |  |  |
| 5 | Peri-Operative | Clinical sites |  |  |
| 6 | Follow-Up form: 1 month; 3 month; and 6 month (both Hip and Knee)\* | CCC (Statix) |  |  |
| 7 | Coordinator training log | CCC |  |  |
| 8 | Delegation log | Clinical sites |  |  |
| **Case Report Forms (CRFs)/Source Documents** | | | | |
| 9 | Electronic Data Capture (EDC): Confirm that all CRFs have been completed and entered into the Statix database | Clinical sites |  |  |
| 10 | Confirm that appropriate source documentation is present for all subjects, as applicable. | Clinical sites |  |  |
| 11 | Confirm that all electronic queries issued to date have been appropriately resolved and closed, where applicable | CCC |  |  |
| 12 | Perform database lock | CCC/Statix |  |  |
| **Adverse Event (AE) and Serious Adverse Event (SAE) Reporting/Reconciliation** | | | | |
| 13 | Confirm that all required follow-up documentation has been retrieved and is present in both the study files, and has been uploaded to the Statix database. | Clinical sites |  |  |
| 14 | Ensure that all AEs and SAEs have been captured, per protocol, and reported to the appropriate parties (Statix and/or local/central IRB) according to reporting requirements. | Clinical sites |  |  |
| 15 | Confirm that all required follow-up documentation has been provided by clinical sites, organized and provided to the OAC. | CCC |  |  |
| **Regulatory Compliance** | | | | |
| 16 | Confirm that signed consent forms are on file for all subjects | Clinical sites |  |  |
| 17 | Ensure all required documents are present and appropriately organized, including (but not limited to):   * Investigator’s Curriculum Vitae(s) * Protocols and amendments * Informed Consent documents * IRB approval letters for the protocol, amendments, Informed Consents, Continuing Reviews, and any other IRB-approved documents * All IRB correspondence | CCC |  |  |
| 18 | Ensure all required documents are present and appropriately organized, including (but not limited to):   * Investigator’s Curriculum Vitae(s) * Protocols and amendments * Informed Consent documents * IRB approval letters for the protocol, amendments, Informed Consents, Continuing Reviews, and any other IRB-approved documents * All IRB correspondence * All CCC correspondence * Delegation log | Clinical sites |  |  |
| 19 | Sites using Central IRB: Ensure reporting of study closure to the IRB and receipt/filing of study closure confirmation; distribute a copy of letter to all clinical sites  Sites using local IRB: Ensure reporting of study closure to local IRB, a copy of which must be forwarded to the CCC | CCC |  |  |
| 20 | Confirm that all protocol deviations have been noted and reported to the local and/or central IRB as appropriate | Clinical sites |  |  |
| 21 | Refer to institutional requirements in placing study documents and materials in long-term storage | Clinical sites |  |  |
| 22 | Confirm requirements for record retention and obtain confirmation when study files will be transferred to long term off-site storage at participating sites | Clinical sites |  |  |
| 23 | Training Log | CCC |  |  |
| 24 | If study was terminated early, confirm clinical sites are in possession of notification of study termination. | CCC |  |  |
| 25 | If study was terminated early, confirm notification of study termination has been sent to all enrolled subjects as appropriate | Clinical sites |  |  |
| **Analysis, Manuscripts, and Submissions/Publications** | | | | |
| 26 | Data analysis complete | DCC |  |  |
| 27 | Primary manuscript finalized | PI/DCC |  |  |
| 28 | Results submitted to ClinicalTrials.gov | CCC |  |  |
| 29 | Update ClinicalTrials.gov with the change in study status | CCC |  |  |
| 30 | Confirm that notification has been made to PCORI and MUSC’s Office of Research and Sponsored Programs (ORSP) for change in study status and update to ClinicalTrials.gov | CCC |  |  |

1. Refer to the University of Washington’s Rivaroxaban Drug Interaction Potential table at <https://depts.washington.edu/anticoag/home/content/rivaroxaban-drug-interaction-potential> [↑](#footnote-ref-1)
2. @ 08/01/2017 [↑](#footnote-ref-2)