Medical University of South Carolina
Clinical Trial Protocol

Comparative Effectiveness of

*P*ulmonary *E*mbolism *P*revention after hi*P* and kne*E* *R*eplacement (PEPPER):

Balancing Safety and Effectiveness

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1. SPECIFIC AIMS

We propose a large pragmatic clinical trial to inform patient choice and balance risk tolerances of individuals who face decisions about different drugs and strategies for deep vein thrombosis (DVT) and pulmonary embolism (PE) prevention after total hip (THA) and knee (TKA) replacement. Indeed, clinical equipoise exists to ethically support such a randomized trial that has great potential to change current practice. We have selected the three prophylaxis methods that represent current orthopaedic practice in North America and collectively account for more than 80% of all hip and knee replacements; a) enteric coated aspirin (regimen with lowest bleeding risk; clinical PE and all-cause mortality rates comparable to more intensive anticoagulants), b) low intensity (INR 1.5-2) warfarin (time honored and one of the most common North American regimens; low bleeding risk [1-2%]), and c) rivaroxaban, a new oral direct Factor Xa inhibitor (regimen with lowest PE and DVT rate but higher bleeding risk [3-5%]). Prophylaxis will continue for 30 days, in accordance with clinical guidelines, and pneumatic compression will be utilized in hospital in conjunction with aspirin, warfarin, or rivaroxaban according to local practice. Each regimen is commonly used in contemporary practice, supported by observational and clinical trial data, and endorsed by the American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons (AAOS) guidelines.[25,26]

1.1. Primary Aims

The Primary Specific Aims of the research are:

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 groups 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. 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. Study site overlap with the FORCE registry is planned.

1.2. Secondary Aims

The Secondary Aims include:

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.[54,55,56]

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 likely outcomes.

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

The current worldwide COVID-19 pandemic has led to the cancellation of many scheduled orthopaedic surgical procedures, including THA and TKA, secondary to shortages of personal protective equipment (PPE) as well as an effort to limit virus exposure of patients and hospital staff.[104] This new health care reality, combined with social distancing and stay at home orders, have resulted in a historic rise in unemployment, affecting insurance coverage and the ability of patients to absorb related co-pays for medical care [105,106]. Collectively these events will have profound and lasting

impacts on the delivery of care. Total joint replacement will likely see a change in volume after this pandemic due to the discretionary nature of this procedure which is impacted by both patient and health care system related factors[104]. Increased susceptibility of older patients to the virus[107,108] and Covid-related propensity for venous thromboembolism (VTE)[109,110,111] will also likely affect patient preferences about proceeding with hip or knee joint replacement surgery.

The intersection of the PEPPER trial and the Covid-19 pandemic provides a unique opportunity to study patient preferences regarding prioritization of high value discretionary procedures like THA and TKA, and how they are influenced by competing life or death health care issues, societal pressures, and major economic stresses. Using an expanded survey developed in conjunction with the PEPPER Patient Advisory Board (PAB), we will conduct a sub-study to assess patient concern over Covid-19 and how this affects intentions to reschedule surgery. We will thus explore the perceived value of these elective procedures, thereby informing expectations for future utilization of discretionary healthcare services. This will not interfere with the original study design and will amplify findings on patient preferences.

Specifically, we will study the cohort of patients enrolled in the PEPPER trial and scheduled for THA or TKA prior to the national pause in elective surgical procedures through deployment of an expanded survey to better understand effects of Covid on patient preferences for, and outcomes following, discretionary joint replacement surgery. We will compare patient reported mental health and surgical outcomes in pre- and post-Covid cohorts as well as VTE events in Covid patients who subsequently undergo THA/TKA. In addition, we will analyze surgical cancellation rates and rescheduling lags over the 12 months following resumption of elective procedures post-Covid at PEPPER study sites. It is anticipated that this enhancement will be accomplished in parallel with the second half of the PEPPER trial and will not otherwise delay its anticipated completion.

Covid-19 Sub-Study Specific Aims

1) *To assess patient enthusiasm for pursuing previously scheduled elective THA/TKA after the Covid pandemic.* By canvassing PEPPER patients who completed enrollment and had surgery cancelled we will assess a pandemic's effects on the value patients place on elective discretionary surgery and their utilization of orthopaedic care. A supplemental survey developed in conjunction with the PEPPER Patient Advisory Board (PAB) will be sent via mail or email and completed by PEPPER enrollees whose procedure was cancelled due to Covid (estimated 300 patients; 2 months of "paused" surgical preop enrollees).
2) *To assess the delay in rescheduling and the rate of "failure to reschedule" surgery for patients who were enrolled in PEPPER and had surgery cancelled due to Covid.* Patients enrolled in PEPPER who had surgery prior to Covid-19 will provide a baseline cancellation rate compared to PEPPER patients whose surgery was cancelled from Covid. Post-Covid "failure to reschedule" rates and rescheduling delays will be computed out to 1 year to account for seasonal scheduling preferences of patients. This will inform our understanding of utilization of healthcare services for elective procedures post Covid. Patient preferences will be assessed from deployment of the PEPPER PAB endorsed survey.
3) *To assess the relative risk of venous thromboembolism (VTE) and anticoagulant-related morbidity in Covid-exposed, recovered, and/or vaccinated patients undergoing THA/TKA.* Evidence suggests an association of hypercoagulability and anti-phospholipid antibodies with Covid disease,[6,7,8] which may increase risk of VTE after THA and TKA. We will investigate the impact of this relationship on VTE after THA/TKA.
4) *To compare patient-reported outcomes (PRO) in cohorts having surgery before and after COVID.* Validated functional outcome tools will be compared among patients before and after COVID, including the Mental Component Score from the PROMIS-10 and the GAD-2 as a marker of psychological distress. This will provide insight into how the Covid healthcare crisis may have impacted patient attitudes and its impact on PRO scores and VTE in a cohort of THA/TKA patients.

Patients involved in the Covid-19 Sub Study will complete the survey under a waiver of written consent. The survey will contain a written statement describing the reason for the survey and the research.

2. BACKGROUND AND SIGNIFICANCE

2.1. Background

Osteoarthritis is the most common form of arthritis and involvement of the hip and knee is a leading cause of long-term disability and time missed from work. The societal burden of this condition is substantial. Elective total joint replacement of the hip (THA) and knee (TKA) comprise the most commonly performed procedures in the US, totaling nearly 1 million annually. Moreover, THA and TKA are increasing in number with the aging of the baby boomer generation and collectively stand out as the single largest expenditure for Medicare. Readmission to the hospital within 90 days of operation occurs after 10-15% of elective hip and knee replacements and venous thromboembolism (VTE; blood clots in the veins), specifically pulmonary embolism (PE; blood clots in the lung), is one of the most common causes.[1-10] Despite advances in surgical and perioperative care, fatal PE occurs in 0.1 to 0.5% of patients and is responsible for more than 1,000 patient deaths each year following these operations.[11-13]Appropriately, considerable effort has been directed at identifying the best method to prevent venous thromboembolism in these patients. However, use of potent anticoagulants soon after orthopaedic operations to reduce the risk of blood clots must be tempered by consideration of the bleeding risk implicit in these procedures. Orthopaedic surgeons typically opt for one of three main regimens for preventing these clots, and guideline recommendations for use of blood thinners have historically been conflicted. The ideal prophylaxis will represent a balance between the risk of fatal pulmonary embolism and the morbidity of bleeding resulting in a hematoma (old blood accumulating in the wound)[14-16] or secondary infection related to anticoagulant use. Such a critical decision requires clear and definitive evidence about the potential benefits and harms of blood thinners used to prevent clots after operation, as well as knowledge of individual patient preferences about these tradeoffs and risks.

Not surprisingly, based on the remarkable success and popularity of total hip and knee replacement, its unique tendency to stimulate blood clot formation, and the substantial cost to Medicare for these operations, several Federal agencies and public entities have emphasized the importance of venous thromboembolism as a public health issue. The NIH last sponsored a Consensus Conference dedicated to this subject thirty years ago, in 1986.[17] That panel concluded, “for high-risk orthopedic patients undergoing elective hip surgery or knee reconstruction … low-dose warfarin, dextran, or adjusted dose-heparin” was “recommended… for at least 7 days” as prophylaxis. They noted these regimens reduced the rate of clinical PE, but “the lowered death rate from PE, while suggestive, is not statistically significant.” The panel also offered a note of caution; that “warfarin and dextran in commonly used doses can cause complications of operative bleeding and wound hematomas… (which) can be a significant problem in joint replacement patients.”[17] Since then, some type of VTE prophylaxis has become “standard of care” after hip and knee replacement in the US. Yet, a singular “best practice” has remained elusive because of the complex balance between the benefits of PE prevention and the harms resulting from anticoagulant-related bleeding and its associated pain and disability.

There remain substantial gaps in evidence concerning the benefits and harms of anticoagulant use to prevent VTE after hip and knee replacement.[18] In 2003,[19] the NIH Consensus Conference on Total Knee Replacement concluded that, “the effectiveness of anticoagulation for the prevention of pulmonary emboli is unclear” and noted prophylaxis recommendations were based “primarily on the reduction of deep venous thrombosis detected by venography.” They went on, “the vast majority of DVTs following TKR are asymptomatic, and the available data indicate that prophylaxis does not alter the occurrence of symptomatic DVT or pulmonary embolism, although no individual study was large enough to statistically assess effects on the occurrence of PE.” They suggested that “a randomized, placebo-controlled trial of prophylactic anticoagulation that assesses the outcomes of PE, bleeding, wound complications, and death seems warranted.”[19] In 2008 the Surgeon General issued a “Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism” based on its in-hospital and post-discharge morbidity and mortality, which was estimated to account for 100,000 to 180,000 deaths each year in the United States.[20] The report called for research on the benefits and risks of preventive and therapeutic anticoagulation for the elderly and those undergoing total joint replacement. In June 2009, the Institute of Medicine included “anticoagulant therapies (eg low-intensity warfarin, aspirin, injectable anticoagulants) for patients undergoing hip or knee arthroplasty”[21] among its national priorities for comparative effectiveness research. The paucity of adequately powered randomized trials providing credible data for clinically meaningful PE and bleeding events has left guideline workgroups unable to provide useful evidence-based recommendations for VTE prevention.

Historically, clinical guidelines from the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) have long been at odds, resulting in confusion for both patient and physician over optimal management.[22,23] The ACCP, a perennial authority on VTE prophylaxis, issued their first clinical practice

guidelines in 1992. Their guidelines historically relied exclusively on prospective randomized trials and favor potent anticoagulants with a primary endpoint of reducing DVT and PE and a relatively low concern for bleeding.[22] Conversely, the AAOS has placed greater value on specific reduction of *clinical* VTE as a primary endpoint with a competing desire to mitigate surgical complications related to bleeding that may result in wound hematoma, re-hospitalization, re-operation, and removal of the joint prosthesis secondary to deep infection.[23,24] In 2009, after specific recommendation *against* the use of aspirin by the ACCP, the AAOS first released clinical guidelines endorsing aspirin for patients at "typical" risk of VTE after hip and knee replacement and introduced an algorithm for risk stratification of patients.[23,24] Aspirin was not recommended for patients perceived to be at "elevated" risk of VTE in favor of more potent anticoagulants and, for patients at "elevated" risk of bleeding, potent anticoagulants were omitted in favor of aspirin, warfarin, or mechanical compression devices alone. For patients with an "elevated" risk of *both* VTE and bleeding, less potent anticoagulant prophylaxis was recommended. The AAOS has consistently endorsed less intensive anticoagulation with aspirin or low intensity warfarin based on observational studies; both agents have been associated with comparable rates of clinical PE and less bleeding than more potent anticoagulants. From the surgeon's perspective, increased bleeding is at least as worrisome as increased risk of PE; indeed, fatal PE occurs substantially less often than does untoward bleeding. Ultimately, reconciliation occurred with release of the 2nd AAOS[25] and 9th ACCP[26] clinical guidelines, with both groups conceding that *clinical* VTE and PE was the important endpoint and insufficient data existed to endorse any specific prophylaxis regimen as "best practice". Perfect harmony was achieved in 2014 when the American College of Surgeons Surgical Care Improvement Project (SCIP) added aspirin to its list of acceptable VTE prophylaxis agents. All groups now decline to endorse a preferred regimen for VTE prophylaxis after THA and TKA, other than to recommend doing *something* to mitigate the risk of thrombosis following activation of the clotting cascade caused by these procedures.

At an international multidisciplinary workshop convened in 2011 by the PI (vdp) of this trial to gain stakeholder opinion on the subject of VTE prophylaxis after hip and knee replacement (Appendix A), the consensus among both surgeons and thrombosis experts was that clinical equipoise existed due to a paucity of data. Notwithstanding the large size of administrative datasets and national joint replacement registries, the observational nature of such data limits the meaningful information that they contribute to this discussion. Opinion leaders from both medical and surgical communities argued for conducting a large definitive clinical trial to better inform future treatment decisions. Shortly thereafter, in March 2012, the AHRQ released an exhaustive Comparative Effectiveness Review[27] on VTE prophylaxis in orthopaedic surgery and suggested "there are inadequate data to say whether or not deep vein thrombosis causes pulmonary embolism or is an independent predictor of pulmonary embolism. The balance of benefits to harms is favorable for providing prophylaxis … and to extend the period of prophylaxis beyond the standard 7-10 days."[27] While the report offered that low molecular weight heparins were superior to unfractionated heparin, an agent abandoned for orthopaedic VTE prophylaxis decades ago, it concluded that "other interclass comparisons either could not be made due to lack of data, showed similarities between classes on outcomes, or had offsetting effects where benefits of one class on efficacy was tempered by an increased risk of bleeding."[27] They recommended that comparative clinical trials should focus directly on final health outcomes rather than DVT as a surrogate and "include more outcomes assessing harms such as bleeding leading to infection, bleeding leading to transfusion, readmission and reoperation to provide more information for the comparative balance of benefits to harms."[27] In keeping with the convergence of ACCP and AAOS guidelines, the Joint Commission[28], Center for Medicare and Medicaid Services[29], and the Surgical Care Improvement Project (SCIP)[30] all now mandate VTE prophylaxis after THA and TKA but none endorse any regimen as "best practice".

Central to this impasse is the acknowledged absence of both clinical VTE and health outcomes endpoint data along with an increased appreciation of the morbidity associated with adverse bleeding events, particularly as perceived by the patient and highlighted by the recent ACCP guidelines.[31] Each of these events occurs so infrequently that nearly 25,000 patients would be needed to derive statistically valid conclusions from a single clinical trial, and no existing studies satisfy this requirement of scale. As a result, specific recommendations to guide patients and physicians in making critical decisions regarding perioperative VTE prophylaxis after hip and knee replacement remain elusive. The ideal prophylaxis represents a balance between the risk of VTE, including death from PE, and the morbidity of bleeding complications associated with anticoagulation used to prevent VTE (table). Most physicians focus on prevention of fatal PE, orthopaedic surgeons desire at least equally to avoid untoward bleeding, and patients invoke less well-represented concerns about quality of life and eventual function indirectly related to both issues. The specific preferences and risk tolerances of individual patients greatly influence the choice of anticoagulant that carries a risk of bleeding and the potential to compromise function. It is logical, therefore, that one patient might elect a less potent anticoagulant such as aspirin, which has a slightly greater risk of death from PE but with the benefit of a greatly reduced likelihood of bleeding,

while another might choose a potent anticoagulant that maximally reduces the risk of death from PE despite a higher risk of related bleeding. There are few more compelling scenarios demanding genuine consideration of outcomes important to patients than an elective operation with a track record of dramatically improving quality of life that also carries a small, but real, risk of death and a greater risk of associated complications that compromise function. A recent report on the risk-benefit tradeoffs that must be considered in electing to undergo TKA vividly illustrates the complex decision analysis faced by more than one million patients each year in the US who undergo total joint replacement.[31a]

2.2. Significance

Our purpose is 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 insufficient sample size, 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 define an optimization function to 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.[31,32]

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. Nevertheless, byproducts of the pandemic have made use of warfarin more challenging; home health nursing to provide in-home blood draws is much harder to find, outpatient labs providing these services are inconvenient and not favored by patients, and severe financial constraints on the healthcare system have made these services increasingly unreimbursed by health insurance. 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.[33] A substantial quality benefit would 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.

2.3. Preliminary Studies

Despite considerable research on new anticoagulant drugs since the last NIH conference on VTED in 1986, the evidence for prevention of fatal PE after THA and TKA has changed very little. Randomized clinical trials demonstrate a progressive reduction in DVT without a parallel reduction in fatal PE. Newer agents (low molecular weight heparins,[58-61] synthetic pentasaccharide, and direct factor Xa[10,62-64] and thrombin[65,66] inhibitors) have exhibited improved efficacy in reduction of venographic DVT when utilized as prophylaxis after THA and TKA but are uniformly associated with incrementally increased peri-operative bleeding risk.[67,68] These trials are powered inadequately to discern a statistically significant difference in bleeding events and are often conflicted by a bias related to industry funding. Conversely, low intensity warfarin (INR 2.0) and aspirin have each been associated with a prevalence of venographic DVT that is up to 5 times greater than with the newer agents, but have comparable clinical PE rates with the benefit of major bleeding complications that are two to three-fold less than with more potent anticoagulants.[7,69-74] Three publications prior to FDA approval of rivaroxaban describe orthopaedic VTE prophylaxis patterns.[75,76,77] A survey of 465 members (55%) of the American Association of Hip and Knee Surgeons (AAHKS) noted 47% of surgeons used warfarin, 28% low molecular weight heparin, and 20% aspirin.[75] A survey mailing to 3,025 general orthopaedic surgeons attracted 634 (21%) respondents.[77] Performing an increasing number of joint replacements was associated with a progressively smaller likelihood of using low molecular weight heparin; from a high of 75% among surgeons performing less than 64 cases per year to a low of 57% among those doing more than 140 per year.[77] With FDA approval of direct oral factor IIa and Xa inhibitors that require no monitoring, rivaroxaban is the most rapidly growing agent for VTE prophylaxis in the US, but reports of increased bleeding and reoperation have curtailed orthopaedic enthusiasm.[62-64,78,79] It is likely that the recent availability of specific anticoagulant antidotes will further increase the popularity of the family of IIa and Xa inhibitors.[79a]

The choice of warfarin and rivaroxaban as comparators for this clinical study are sound and supported by the lowest reported VTE event and all-cause mortality rates. Warfarin is a proven agent with the longest track record in orthopaedic VTE prophylaxis and many believe, despite the inconvenience of monitoring,[80] that it continues to represent the best available compromise between efficacy in preventing clinical PE and safety in minimizing adverse bleeding. Low intensity (INR 2.0) warfarin continued for 4-6 weeks after total joint arthroplasty has been associated with readmission for VTE complications of 0.3% after hip[7] and 0.2% after knee[8] arthroplasty and a major bleeding rate of only 0.1%. Low intensity anticoagulation after discharge rarely results in readmission or death[7,8,11,69,72,73,81] but major hemorrhage may do so, especially if intracranial, intraocular, or into the joint causing skin slough and secondary deep infection.[54,68,71] In contrast, rivaroxaban is thought by many to represent the future of orthopaedic VTE prophylaxis; it was the most rigorously studied agent prior to release[10,62-64], is highly effective in reducing PE and venographic clots, is taken orally, and requires no monitoring. Its primary drawback was initially the absence of a known antidote and bleeding events exceeding that of low molecular heparins,[78,79] which made it less popular among some surgeons. It is now likely that the recent availability of specific anticoagulant antidotes will further increase the popularity of the family of IIa and Xa inhibitors.[81a] However, some authors have demonstrated increased all-cause mortality with potent anticoagulants, such as low molecular weight heparin, more than twice that of patients receiving aspirin and pneumatic compression combined with regional anesthesia.[54] In the same study, patients receiving low molecular weight heparin developed nonfatal pulmonary embolism 60-70% more often than those receiving aspirin and compression,[54] indicating that clinical PE occurs despite prophylaxis with potent anticoagulants[9,55] and should never be considered a “never event”[20,29,30]. Other authors have reported the “failure” of low molecular weight heparin prophylaxis; symptomatic DVT (3.8%),

nonfatal PE (1.3%), persistent wound drainage resulting in readmission (4.7%) and reoperation (3.4%) occurred at rates exceeding prior experience with low intensity warfarin.[58] Not surprisingly, the orthopaedic community has been slow to adopt routine use of these newer agents and has favored a more balanced strategy that offers a lesser bleeding risk with comparable protection against clinical VTE events.[6,75,82]

Aspirin, or acetylsalicylic acid, has been used in conjunction with mechanical compression devices for VTE prophylaxis by a minority (10-20%) of surgeons and historically has been considered to have effects largely on the arterial circulation. As such, its choice as a comparator deserves some discussion. It is conventionally thought to reduce the propensity for arterial thrombosis through inhibition of platelet cyclooxygenase-1, which, in turn, decreases synthesis of thromboxane A2 (platelet-activating eicosanoid) and related platelet activation. Platelet aggregation and adhesion have long been considered important variables of thrombosis in the high-flow, high-shear arterial circulation. Consistent with this mechanism, large longitudinal clinical studies have demonstrated substantial arterial thrombotic event reduction and survival benefit relative to stroke, myocardial infarction, and related deaths in high-risk patients. Conversely, many clotting experts regard aspirin as an inferior agent in mitigating *venous* thrombosis, where fibrin-rich clots are the more common result of prevalent low flow and low turbulence conditions. From a mechanistic viewpoint, some doubts concerning the efficacy of aspirin may derive from variability in preparations used. The degradation of aspirin with release of acetic acid over time is well known. Less well known is the phenomenon of "pseudoresistance" due to variability in absorption of enteric coated aspirin, which is far more common than any true resistance.[83] Secondary analyses of administrative data and some older investigations did not have quality control of the aspirin supply or documentation regarding enteric coating. To assure test sensitivity in our trial, we will ensure that patients assigned to treatment with aspirin make use of fresh supplies of enteric coated tablets.[83] In most settings, hematologic consultation for VTE prophylaxis typically yields a recommendation for use of traditional anticoagulants such as vitamin K antagonists, heparin derivatives, or the newer direct factor Xa or IIa inhibitors. Accordingly, aspirin has had a checkered history in the arena of prevention of VTE; this erratic past is particularly evident from the perspective of the orthopaedic community. In 1977, Harris and colleagues first suggested that aspirin (600mg bid) reduced the risk of deep venous thrombosis, as assessed by contrast venography, following total hip arthroplasty.[84] Inconsistent effects in men and women, variable dosing regimens, and differential effects with general compared with regional anesthesia lead the 1986 NIH consensus conference to conclude that aspirin had no role in VTE prophylaxis after hip and knee replacement, and the orthopaedic and thrombosis communities continued their search for the ideal agent. Fueled largely by increased bleeding with all of the newer agents, aspirin remained in use by a cautious minority based on its low rate of bleeding complications. No randomized clinical trial of aspirin for VTE prophylaxis after THA and TKA exists, yet the Pulmonary Embolism Prevention (PEP) trial compared clinical morbidity and 35 day mortality in 17,444 patients receiving aspirin or placebo for VTE prophylaxis after either repair of hip fracture, THA, or TKA.[85] Aspirin patients experienced an overall VTE rate of 1.15% compared with 1.4% in patients receiving placebo, but 13,356 of the patients underwent surgery for hip fracture repair and only 4,088 had elective joint replacement. In part encouraged by these favorable results, several large observational studies[86,87,88] have reported comparable readmission rates for clinical PE and DVT after THA and TKA when aspirin was used as primary VTE prophylaxis, especially with use of regional anesthesia for the index arthroplasty procedure. The adjunctive use of pneumatic compression to augment venous return and increase fibrinolysis as an approach to VTE prophylaxis is now popular in orthopaedics, especially in combination with aspirin, because of a favorable safety profile without an increase in bleeding risk.[12,23,24,77,89,90] However, just as less intensive anticoagulation was gaining in popularity, a recent randomized trial comparing aspirin with warfarin according to AAOS guidelines for VTE prophylaxis was discontinued prematurely due to a clinical PE rate nearly eight fold greater in the aspirin group.[91] Notwithstanding this negative report, there are provocative new data supporting a mitigation of VTE by aspirin.

In 2012 two important prospective randomized clinical trials were published concerning the use of aspirin to prevent recurrent VTE. In both the *Aspirin for the Prevention of Recurrent Venous Thromboembolism* [Warfarin and Aspirin (WARFASA)][92,93] study from Italy and the *Aspirin to Prevent Recurrent Venous Thromboembolism* (ASPIRE)[94,95] trial from Australia, patients with a first episode of unprovoked VTE within two years of enrollment were randomized to receive either aspirin 100 mg daily or placebo after completion of at least 6 weeks of standard oral anticoagulation with warfarin. In the WARFASA trial, which included 402 patients, aspirin reduced the risk of recurrent VTE from 11.0% to 5.9% (hazard ratio .55; p=0.02) over a median treatment of nearly two years.[92] The ASPIRE trial[94] included 822 patients and recurrent VTE was noted in 6.5% assigned to placebo compared with 4.8% receiving aspirin (hazard ratio 0.74; p=0.09) over a median follow-up of 37 months. Despite the non-significant reduction in recurrent VTE in ASPIRE, patients on aspirin enjoyed a reduction in a composite of major vascular events (overall VTE, myocardial infarction,

stroke, or cardiovascular death) from 8.0% to 5.2% per year (hazard ratio 0.66; p=0.01). Similarly, patients receiving aspirin experienced an overall net clinical benefit (aggregate of recurrent VTE, myocardial infarction, stroke, major bleeding, all-cause mortality) with an event rate reduction from 9.0% to 6.0% per year (hazard ratio 0.67; p=0.01). In both studies there was no difference in major or non-major bleeding events between groups. Considering these two trials together, aspirin was associated with a 32% reduction in recurrent VTE (hazard ratio 0.68, p=0.007) and a 34% reduction in major adverse vascular events (hazard ratio 0.66; p=0.002), without an increase in bleeding.[95] This combined efficacy of aspirin in preventing VTE without a compromise in safety challenges the traditional view of its arterial only mechanism and might legitimately stimulate a re-evaluation of its role in orthopaedic VTE prophylaxis.

3. RESEARCH DESIGN AND METHODS

The proposed clinical trial is highly *patient-centric* by virtue of the information it seeks to provide about patient preferences and patient reported outcomes (PRO) for general well-being and joint-specific function associated with various VTE prophylaxis regimens, which is arguably the critical missing link in this conversation. This trial will be most influential by elucidating the variable preferences of patients relative to prevention of PE, avoidance of bleeding, and the impact of these outcomes on eventual function. The study exemplifies the five features of patient-centered outcomes research (PCOR); it assesses the comparative benefits and harms to patients of currently utilized regimens for VTE prophylaxis after THA and TKA, as performed in a variety of real-world settings, based on patient-reported outcomes of function and general well-being with design and analysis guided by patients and advocacy group stakeholders. The trial is focused on the principles of PCOR and addresses three questions that are of importance to patients: 1) patient reported outcomes will be linked to adverse VTE/PE and bleeding events to ascertain potential interdependence; 2) the patient-perceived value proposition between prevention of VTE/PE and avoidance of bleeding complications will be assessed by a community lay person survey, a past and prospective patient questionnaire, and patient advisory board (PAB) review facilitated by a physician expert in patient preferences in medical treatment; and 3) study findings will be interpreted by the PAB both independently and in concert with the steering committee to provide unique patient and clinical investigator perspectives on study findings as a basis for final consensus recommendations.

1) Patient-reported outcomes (PROs) will be utilized to assess joint-specific function of hip and knee replacements as well as general health status as they relate to type of VTE prophylaxis and the occurrence of primary study endpoints and adverse events. All sites in the PEPPER trial will collect baseline comorbidity, joint function, and general well-being and global health data at time of enrollment and at 4 weeks (+10 days), 3 months (+/- 10 days), and 6 months (+/- 1 month) following surgery. Medical comorbidity will be reflected in the patient-reported Charlson index, spine-specific musculoskeletal comorbidity will be captured with a single Oswestry instrument question, and joint-specific function will be captured using the patient-reported hip and knee disability and osteoarthritis outcome scores (HOOS and KOOS, respectively). General well-being and global health will be assessed with the Patient Reported Outcomes Measurement Information System (PROMIS). The Charlson index[34,35], Oswestry[36], HOOS,[37] KOOS,[38] and PROMIS-10[38a] are all previously validated PRO tools for clinical assessment. The customized patient questionnaire (Appendix B) interrogates the occurrence of primary effectiveness and safety events specific to this study, and incorporates elements of the PROMIS-10 global health surveys, the Charlson and Oswestry instruments, plus either the HOOS or KOOS short form physical function tool, as applicable. These data will be analyzed in patients having endpoint outcomes of PE/DVT, adverse bleeding events, and reoperation, as well as a 20% random sample of those who do not, in order to uniquely elucidate the impact of these events on eventual joint-specific function and general patient well-being. These findings will also be externally validated through collaborative historical data collection and exchange with the AHRQ sponsored FORCE joint replacement registry; notably, several FORCE core centers will participate in the proposed trial. Level of function, as well as change in function after operation, will be compared among patients who experience primary endpoint events and those who do not, as well as with baseline data from the AHRQ FORCE joint replacement registry, which has collected four years of functional outcomes after hip and knee replacement in over 30,000 patients.[39] *No prior VTE prophylaxis study has considered the impact of VTE outcomes or related adverse events on patient-reported joint specific function and general well-being; this novel information will further inform patient choice of VTE prophylaxis by introducing tradeoffs for functional outcome into the value proposition balancing PE prevention and bleeding risk.*

2) Secondly, we will ascertain the patient's value proposition in the risk-benefit tradeoff between prevention of VTE and PE, and the downside risk of untoward bleeding implicit in use of anticoagulant prophylaxis. A Dartmouth community survey following an educational seminar suggests that the lay public may fear a 2-5% risk of bleeding,

reoperation, and infection more than they fear a 1 in 1,000 risk of death from PE after joint replacement.[40] Similarly, an IRB-approved questionnaire (Appendix C) was utilized to assess prospective and past joint replacement patients' preferences regarding the tradeoff of PE prevention and bleeding for several months prior to submission of this application; this information validated prior assumptions and guided design of the proposed trial. Finally, a subset of patients enrolled in the trial will participate in a conjoint analysis exercise to explore risk tolerance for specific outcomes: death from PE; symptomatic PE/DVT; bleeding leading to delayed wound healing, pain, and stiffness; reoperation to drain a collection of blood from the wound; and infection necessitating removal of the implant. Patients will review and rate orthogonal sets of alternatives with varying probabilities over the plausible range of each outcome to assess the value proposition of relative likelihood of the different adverse events.[41] Any apparent inequality in seriousness of paired outcomes will be balanced by relative likelihood of each; fatal PE is a 1-2 in 1,000 event compared to the aggregate of bleeding and reoperation, which is a 1-5 in 100 event. As seen in both the Dartmouth community survey and the pre-application patient questionnaire, it is anticipated that this information will reveal an underappreciated risk aversion of patients for bleeding events because they are less common than VTE/PE and negatively impact recovery and eventual function after operation. We believe that physicians and payers disproportionately value in-hospital VTE and adverse safety events because they do not witness the more subtle compromise in function and patient well-being that does not result in death or readmission. These outcomes are typically more insidious in their presentation, occur after hospital discharge, and are more apparent to the patient and surgeon than to guideline authors. This information will inform non-patient stakeholders about what patients perceive as the greatest threat to their well-being; potentially fatal thromboembolism or bleeding that can result from aggressive perioperative anticoagulation efforts to prevent VTE.

3) Finally, we have assembled an innovative multi-purpose Patient Advisory Board (PAB) to assist in formulating techniques for data collection as well as strategies for critical determination and analysis of patient-perceived relative importance of the observed study findings. Composition of the PAB will be addressed in greater detail later in this protocol. The PAB will serve a critical role in a three-tiered analysis ensuring patient centricity in the study. First, the PAB will provide analysis of the relative importance of primary safety and effectiveness endpoints from the patient's perspective, based on the patient intake conjoint analysis risk tolerance survey for bleeding and thromboembolism, to create an aggregate weighting of benefits and harms representative of patients enrolled in the trial. 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. The second tier function of the PAB will be to 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 aggregate analysis of pre-operative risk tolerance and observed functional outcomes will result in an overall preference weighting of each prophylaxis regimen based on observed benefits and harms. This effort will be inevitably and intentionally influenced by personal experiences of each individual panel member and facilitated by a physician expert in assessment of patient preferences in medical care and treatment. Finally, the PAB will provide a third tier independent review of final study results and event rates associated with each prophylaxis regimen in the context of non-inferiority 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. It is expected that preferences for each prophylaxis regimen will vary according to the predominant risk aversion of any individual patient and the PAB will be best positioned to interpret and process those differences. There is compelling evidence from other areas in medicine, where several alternatives can be appropriate for different persons, that patients and providers can substantially disagree on both the importance of critical facts and treatment goals. One striking example involving decisions about surgical treatment for breast cancer noted that 71% of treating physicians prioritized saving the breast compared with only 7% of their patients.[42] We suspect that a similar gap may exist between patients and their doctors regarding VTE prophylaxis after hip and knee replacement. A major contribution of this study will be elucidation of the value proposition driving patient preference of VTE prophylaxis, and how it may differ from those of the patient's surgeon and medical physician, including how patient socioeconomic characteristics such as education and ethnicity might influence those choices.

Finally, dissemination of this information to patients and other stakeholders will be essential to informing, and potentially transforming, the use of VTE prophylaxis after THA and TKA. In addition to the usual scholarly papers, we will

produce and distribute educational materials through social media, patient advocacy groups (North American Thrombosis Forum and the National Blood Clot Alliance), professional societies of non-patient stakeholders (The Hip Society, Knee Society, American Association of Hip and Knee Surgeons, and Orthopaedic Research Society), and organizations responsible for clinical guidelines (ACCP and AAOS), all of which are engaged as members of the trial steering committee. Also, the American Association of Retired Persons (AARP) has expressed interest in communicating study findings to their members and constituents after final data analysis and messaging have been determined.

3.1. 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 *will not be inferior to* low intensity warfarin (INR 2.0) or 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 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 indication only.

The proposed study period will now encompass approximately 10 years: 9 mos for preliminary work; 97 months of patient enrollment; 6 mos trailing follow-up after closure of enrollment; and 6 mos final data analysis. Each site will enroll approximately 1,000 patients over three years for an average annual site enrollment of 333 patients. Each site will aim to reach this goal of 1,000 patients with recruitment continuing at all sites until the overall study enrollment goal is met. 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 planned lifetime follow-up, the study will result in enrollment of 18,829 patients with complete follow-up for primary outcome endpoints in approximately 18,000. 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.

Covid-19 Sub-Study

For most patients, only one additional contact will be required to accomplish the proposed enhancement but this supplemental investigation will not hinder, alter, or interfere with ongoing operations of PEPPER. This incremental data collection will easily integrate with ongoing PEPPER processes and will complement existing data files and patient preference analyses regarding VTE and risk tolerance relative to anticoagulant choice as well as pursuit of discretionary surgery. Active enrollment in the PEPPER trial is now on “pause” until elective THA and TKA are resumed at the participating sites, which began at some sites as of May 4, 2020. During this hiatus, patients whose scheduled procedures have been postponed can still be accessed for the proposed baseline data collection and follow-up on this study cohort will occur with the restart of elective surgeries.

Recruitment Plan

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 (18% of screened)	20,000
Target sample size with complete follow-up (accounting for 10% loss to follow-up)	18,000

3.1.1. Participating Sites

Approximately twenty-five field sites have been identified and have committed to randomization of patients to the treatment groups. Each site has been selected based upon the expertise of the operating surgeons in total joint replacement, the commitment and culture of the institution to support high quality clinical research, a past history of institutional involvement in clinical data collection with a high degree of reliability and accuracy, and the ability to recruit sufficient patient numbers to meet enrollment targets. Each of the included sites has been successfully involved in clinical trials in the past.

The consortium of approximately 25 study centers accounts for 37,550 THA and TKA per year, resulting in a conservative projected enrollment rate of 18% (20,000/112,650) of all procedures performed. Previous elective surgical trial enrollment rates from these sites has ranged from 33% to 60%, and a pre-application patient survey (Appendix C) suggests that more than 50% of patients undergoing elective THA/TKA would be willing to be randomized. We projected a pre-Covid 22% recruitment yield with confidence because our clinical sites have track records this good or better and, as a pragmatic clinical trial, PEPPER has no placebo groups, all interventions are currently accepted treatments, and PEPPER has avoided both profusion and complexity of eligibility criteria, which are usual reasons for failure to recruit adequately in clinical trials.

3.1.2. Study Procedures

In May 2023, PCORI approved the removal of the warfarin arm of the trial due to increasing institutional barriers, such as the prevalence of home health and the inability to receive INR testing, owing to the pandemic. All patients enrolled after the approval of this protocol and all subsequent site-specific approvals will use a 1:1 rivaroxaban: aspirin randomization scheme. Patients who were enrolled and randomized into the warfarin arm of PEPPER prior to this protocol approval will remain in the trial, continue to receive warfarin, and be followed for data collection as needed per the protocol. The data collected on all warfarin patients will be analyzed as described in the analysis section.

a) Screening and Enrollment

Approximately 20,000 eligible patients undergoing elective primary or revision hip or knee joint replacement will be enrolled at approximately 25 centers. Initial screening will occur of all consecutive patients scheduled for elective total hip or knee replacement in the practices of participating surgeons; while screening criteria will be reviewed by the local study coordinators, physician confirmation will be required before a patient is determined eligible for enrollment into the trial. All consecutive eligible patients will be approached for entry and must agree to randomization to participate in the trial. With a goal of 25 centers enrolling approximately 20,000 patients at a rate of about 1,000 per center over eight years, the rate of enrollment is 267 patients per center per year or 6 patients/week for one study coordinator working 48 weeks/year. Sites may continue to enroll past the 1,000 patient goal until the overall study enrollment goal is met. A signed informed consent form will be obtained before performing any study procedures that go beyond standard clinical care. A subject is considered enrolled when all eligibility criteria have been documented as being met and the institutional consent form (ICF) is signed.

Initial discussion and introduction to the study will occur with the treating surgeon in the course of an outpatient appointment at the time of patient decision to pursue elective THA or TKA, primary or revision. Informational materials about the study can be distributed at this time and the operating surgeon should uniformly endorse participation of all eligible patients in the study. At any point prior to surgery, should the prospective study patient have any questions regarding the procedures of the study, a study staff member and/or the surgeon will answer all questions to the patient's satisfaction.

Participants may be consented using two methods:

1. In-person Recruitment: The PEPPER site coordinator and/or surgeon meets with potential participants in person to review the trial and obtain informed consent and signed documents through paper consent forms or e-consenting via REDCap. A copy of the signed consent form will either be given in person, mailed, or emailed to the participant based on their preference. If the patient remains uncertain about participation, the site coordinator and/or surgeon will contact the patient by phone or video conference to further develop understanding and confidence of the patient to participate in the trial;
2. Remote Recruitment: Remote recruitment will occur either when a potential patient has requested more time to review the study or when the patient is not seen during an in-person surgical clearance visit. The potential participant must have the appropriate capabilities to access REDCap (i.e computer, smartphone, or tablet, and an internet connection) and must be in a private location during the consenting process. The coordinator or designated study staff will contact the patient either via phone or video conferencing. The informed consent process will be completed with signatures of all parties obtained via e-consent using REDCap. The signed consent form will then be either emailed or mailed to the participant based on their preference. Remote consenting can occur up to one day prior to surgery.

If a patient is unable to sign the consent form during a pre-operative clinic visit and does not have the necessary capabilities to utilize e-consenting, written consent may be obtained via telephone. Obtaining written consent over the phone may only be done only if the patient has a paper copy of the consent form. The patient will sign their copy of the consent form while the coordinator signs one as well. The patient will either mail, email, 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.

Consent to participate in the study may be obtained by the study site coordinator or any other appropriately qualified 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 outcome scores (HOOS and KOOS), the Oswestry and Charlson instruments, and the PROMIS-10 global health survey. Baseline instruments should be collected within the 3 months prior to the patient's operation.

Once consent is obtained, the surgeon will sign off on all eligibility criteria using the Surgeon Screening Confirmation Form and the patient will be considered enrolled in the PEPPER trial and eligible for randomization.

b) Inclusion Criteria

The Inclusion Criteria for entry into the trial are as follows:

1) Males and females 21 years of age or older;
2) Undergoing elective primary, resurfacing arthroplasty, revision, or second stage re-implantation total hip replacement;
3) Undergoing elective primary, revision, or second stage re-implantation total or uni-compartmental knee replacement;
4) Patient is eligible for randomization to at least two of the study anticoagulation regimens;
5) Patient has necessary mental capacity to participate and is able to comply with study protocol requirements;
6) Patient is willing and able to give informed consent; and
7) Patient is willing to be randomized and participate.

c) Exclusion Criteria

The Exclusion Criteria for entry into the trial are as follows:

1) Patients undergoing bilateral hip or knee replacement;

2) Patients undergoing total hip or knee replacement who have been enrolled in this study for a prior hip or knee replacement;
3) Patients who are concurrently enrolled in another active interventional clinical trial testing a drug or intervention known or believed to interact with aspirin or rivaroxaban;
4) 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;
5) Patients on chronic (longer than the prior 6 months) anticoagulation other than with antiplatelet medications;
6) Patients with documented gastrointestinal, cerebral, or other hemorrhage within 3 months of the operation;
7) Patients with a known diagnosis of defective hemostasis and past history of clinical bleeding requiring transfusion and treatment;
8) Patients who have had an operative procedure involving the eye, ear, or central nervous system within one month;
9) Patients with severe uncontrolled hypertension with systolic BP > 220mmHg or diastolic BP > 120mmHg;
10) Patients with an absolute body weight of less than 41 kilograms (90.4 lbs) at baseline visit;
11) Vulnerable patient populations including 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.

d) Randomization

Randomization of consented patients occurs after the surgeon confirms eligibility and up until the day before the originally scheduled surgery date. 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.

Patients will be assigned to treatment groups using a web-based randomization system. A permuted block randomization scheme will be utilized to ensure equal assignment of patients to each drug study group at each participating site, taking into consideration the noted criteria for stratified randomization. In the absence of any randomization stratification requirements, patients meeting all eligibility criteria without any randomization exclusions will be assigned to one of two groups; a concealed centralized randomization schedule will provide assignment to one of two prophylaxis regimens (aspirin or rivaroxaban) in randomly varying block sizes developed separately for each clinical site and stratified according to type of surgery (hip or knee replacement). Prophylaxis will continue for 30 days, in accordance with clinical guidelines, and pneumatic compression devices will be utilized in hospital in conjunction with both of the treatment groups according to local practice. The two groups are as follows:

1) Enteric coated aspirin (regimen with lowest bleeding risk; clinical PE and all-cause mortality rates comparable to more intensive anticoagulants); and
2) 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 two study prophylaxis regimens for venous thromboembolism is exclusionary.
The contraindications to aspirin are:

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;
4) Patients with a cancer diagnosis who are under active treatment.

The contraindications to rivaroxaban are:

1) Patients with a serum creatinine greater than 2.0 mg/dl;
2) Patients taking medications that interfere with metabolism of rivaroxaban via CYP 3A4 inhibition.

If, after randomization, a participant is unable to take the specified 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 the other arm of the trial.

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

Please refer to the Manual of Procedures for additional guidelines involving randomization assignments.

e) Study Medication Administration

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.

Rivaroxaban group: Rivaroxaban 10 mg will be first administered approximately 24 hours after completion of the index operation. Medication will then be administered in the evening on postoperative day #2 and thereafter each evening until completion. Patients on cardiac dose aspirin may will continue their regular cardiac dose aspirin if randomized rivaroxaban. Please refer to the Manual of Procedures for specific Rivaroxaban administration timing.

In May 2023, PCORI approved the removal of warfarin from the PEPPER trial. Warfarin medication administration guidelines will no longer apply for patients enrolled after the approval date of this protocol and subsequent site-specific IRB approvals. Dosing for those patients who have previously been randomized to warfarin prior to this protocol approval will be as follows:

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).

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.

f) Follow Up Visits

Study patients will be contacted at 4 weeks (+ 10 days), 3 months (+/- 10 days), and 6 months (+ 3 months/- 1 month) after operation through Statix, LLC, a centralized data collection group located in Salt Lake City, UT. Serial efforts

to obtain follow-up of research subjects through mail, telephone, electronic communication, and web-enabled online surveys will be conducted. 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. Study coordinators will contact the patient and inquire about and confirm any known or suspected VTE outcomes or adverse events reported by the patient by either verification of the local medical record or obtaining the medical record from the outlying facility where the patient was treated. Specifically, readmission to outside hospitals will be confirmed by record retrieval and review by the site coordinator at the study site where the index procedure was performed.

Our experience is that patient reporting of *events* increases yield of data collection;[57] since 1 in 4 readmissions go to facilities other than that of the index procedure, observed *plus* patient reported readmissions will be captured. All centrally identified clinical study endpoint events that are confirmed by on-site coordinator record review and patient interview, will then be adjudicated by an expert panel (Outcomes Assessment Committee; OAC).

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.

Medical record review will be performed on all participants who experience either endpoint events or adverse events (either reported by the patient during follow-ups or following *ad hoc* discovery by site coordinators), and those who fail to otherwise respond to data collection efforts at the 6-month follow up.

A search of the National Death Index will be performed on those patients who have failed to respond to the 6 month follow up and who have not been reported as deceased by any other measure. In order to collect data on any possible deaths, patient identifiers already collected for the PEPPER trial will be submitted to the National Death Index. The National Death Index will perform a cause of death retrieval report for any and all causes of death where applicable. Patient identifiers and subsequent death information will be submitted and shared via a secure SFTP server.

For those sites that have larger populations of Spanish speaking patients, follow up interviews will be conducted by Statix in Spanish. All study documents, including the consent document, HIPAA authorization form, and any paper-based assessments will be appropriately translated and submitted for IRB approval before any Spanish speaking patients are enrolled.

g) 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.[96-98] *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[96] or evidence of a filling defect on invasive contrast venography. PE will be diagnosed on the basis of contrast-enhanced chest computed tomography,[99] 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.

3.1.2.1. Schedule of Events

	Screening	Baseline (-3 months to -1 day)	Randomization (Surgeon Confirmation 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								
Electronic/ 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				X*					
Study Drug Administration (Aspirin Arm)				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

* Urine pregnancy test done as part of the patient's standard of care and the results will be reviewed for research purposes.

3.1.3. Data Analysis

Primary Data Analysis

The unblinded nature of the clinical trial could threaten unbiased comparisons. Randomized patients will not be notified of treatment group assignment until the day of the proposed operation, unless necessary to provide third party insurance coverage for prescribed medical care. Further, our trial is protected from this threat to adherence with treatment assignment by the short course of treatment, the follow-up contact to ascertain treatment, and the motivation of each patient to take prescribed drugs to prevent PE and DVT. The trial is protected from the threat to unbiased outcome ascertainment and classification by the independent centralized contact with patients to determine need for collection of clinical documents, preparation of documents related to readmission or treatment for bleeding or thrombosis to remove any indication of treatment assignment, and blinded outcome classification based upon expert review of the redacted documents by the OAC.

1.0 Primary Aim 1. *To compare the frequency of the aggregate clinical endpoint of important venous thromboembolism (clinical PE and DVT leading to hospital readmission) and all-cause mortality.*

1.1 Risk Estimates. First, 6-month probabilities of our primary composite endpoint (clinical PE, clinical DVT, and all-cause mortality) by treatment group will be estimated and compared. To address the fact that some participants will have incomplete follow-up (e.g., we may know whether they had an event within 3 months but not for the full 6 months), we will estimate 6-month risk of an event using a Kaplan-Meier approach. Confidence intervals will be based on Greenwood's formula (applied using the delta method to a complementary log-log transformation of the estimated risk). In these calculations, those whose follow-up is incomplete will be censored at the time that the follow-up ends.

The ***primary analysis will be a "per-protocol analysis".*** In this analysis, patients will be censored at the time that they switch away from the treatment to which they were randomized. Thus, for example, if a patient was randomized to rivaroxaban and was treated with aspirin instead, they will not be included in the per-protocol analysis. If a patient received the treatment to which they were randomized, but later switched treatments, the patient will be included in the per-protocol analysis up until the time the patient switched, and then censored (as recommended by Hernan and Robins, NEJM, 377:14, 1391-1398).

Note that in our "per protocol analysis", we will still include patients in the analysis who do not completely and fully adhere to the medicine to which they are assigned and treated. Thus, for example, if a patient is randomized to, and treated with, aspirin in the hospital but reports failing to take aspirin in the four weeks after hospital discharge, they will still be included in the analysis. This is because this is a pragmatic trial and the goal is to estimate the risks in a real-world setting. Specifically, our goal is to estimate the risks among those who are prescribed and have access to a particular medication. We recognize that this use of the expression "per-protocol analysis" is not a traditional one, which would typically exclude all those who do not fully adhere to their medication, and can result in a study sample that is not perfectly representative of the study population as a whole. We believe that this lack of representativeness is more acceptable than the bias that would be incurred in an intention-to-treat analysis which would include patients who are not treated with a medication in an analysis of risks among those taking that medication.

In secondary analyses, we will also perform an intention to treat analysis and an "as-treated" analysis. In the intention to treat analysis, patients will be included in the analysis in the group to which they were randomized and only be censored when they are lost to follow-up. However, some patients who are randomized will be excluded from all analyses (See sections 1.3 and 1.4 below). In the "as treated" analysis, patients will be included in the group based on the study medication they actually received. Thus, for example, if a patient is randomized to rivaroxaban but receives aspirin, they will be included in the aspirin group. This approach will include "crossover" patients and provide more precise estimates of what actually happened to patients who took the study medications, but will need to be interpreted with caution as this approach has more potential to result in a lack of representativeness of the groups.

1.2 Treatment Comparisons. Next, each pairwise comparison of the treatment groups (i.e., aspirin vs. rivaroxaban, aspirin vs. warfarin, rivaroxaban vs. warfarin) will be performed separately, only including those patients with no medical contra-indication for either of the two treatments in that pair. In addition, for each pairwise comparison, we will only include those patients who were randomized at sites during a period of time where patients could have been randomized to either of the two treatments being compared. For example, a patient randomized to aspirin at a site restricted to use of rivaroxaban and aspirin cannot be included in an aspirin to warfarin comparison because that patient could not have received warfarin at their respective site (see below).

For each pairwise comparison we will calculate a two-sided 95% confidence interval for the risk difference (i.e., the difference between the groups with respect to risk of the composite endpoint) based on the variances of each estimated 6-month risk calculated by Greenwood's formula. These confidence intervals will be interpretable as the range of differences that cannot be ruled out by a test at the two-sided 5% level. Next, the strength of evidence for non-inferiority of aspirin relative to rivaroxaban with respect to risk of our primary endpoint will be formally assessed by calculating a one-sided p-value for the null hypothesis that the 6-month risk of an event among those in the aspirin group is at least 0.69 percentage points greater than the risk among patients taking rivaroxaban. A low p-value indicates evidence against this hypothesis and would suggest that the risk among those taking aspirin is less than 0.69 percentage points greater than the risk among those taking rivaroxaban. The p-value will based on the test statistic:

$$= \frac{\hat{r}_{aspirin} - \hat{r}_{rivaroxaban} - 0.0069}{\sqrt{VAR(\hat{r}_{aspirin}) + VAR(\hat{r}_{rivaroxaban})}}$$

where $\hat{r}_{aspirin}$ is the estimated risk of events in the aspirin group and $\hat{r}_{rivaroxaban}$ is the estimated risk in the rivaroxaban group. The p-value will be the probability that a standard normal random variable will be less than this value. Note, a one-sided test (rather than a two-sided test) is appropriate for evaluation of a non-inferiority hypothesis[51] and is recommended by Farrington and Manning[100] An analogous statistic will be calculated to compare aspirin to warfarin.

The standard analysis for superiority trials is to base the analysis on the principle of intention to treat. In this analysis, patients are included in the group to which they were randomized, irrespective of the treatment actually received. However, as recognized by the FDA in their guidance [1], in a non-inferiority analysis, the intention-to-treat analysis is biased towards finding non-inferiority because protocol violations and cross-overs tend to diminish

[1] https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf

differences between groups. Therefore, similar to the estimation of risks, the primary analysis of non-inferiority will be based on only on follow-up while patients were treated with the medication to which they were randomized (a per-protocol analysis). We do recognize, however, that the exclusion or censoring of randomized patients from the analysis due to medication switching could result in differences between the groups that will bias their comparisons. To address this possibility, in secondary analyses, the patients will be weighted to adjust for imbalances between the groups with respect to age, sex, site, and education, as described in section 1.5.4 below.

The two-sided confidence interval for the treatment differences will also be used to assess superiority of one treatment over another. If the confidence interval does not overlap 0, then this would be equivalent to statistically significant superiority of one treatment over another at the two-sided 0.05-level. A p-value to summarize the strength of evidence against the null hypothesis that the risk is equal in the two groups can be calculated based on the Z-statistic:

$$= \frac{\hat{r}_{Rx1} - \hat{r}_{Rx2}}{\sqrt{VAR(\hat{r}_{Rx1}) + VAR(\hat{r}_{Rx2})}}$$

where the risks and variances are calculated using the Kaplan-Meier approach and Greenwood's formula.

Finally, comparisons of a composite of the primary effectiveness endpoint, prevention of thromboembolic events, *and* the primary safety endpoint, avoidance of bleeding-related events, will be performed among the three treatment groups. This assessment of "net clinical benefit" (Samama CM et al, NEJM 2020 May 14;382:1916-1925) will consist of comparing a combined measure, the percentage of patients with either a primary effectiveness endpoint (symptomatic DVT and PE plus all-cause mortality) or a primary safety endpoint (aggregate of bleeding complications including major, non-major clinically important, and wound-related) between each pair of treatments. Analyses will be conducted in the same manner as described above.

1.3 Randomized patients who do not undergo surgery. Patients who were randomized but then do not undergo surgery will be excluded from all analysis. This approach is consistent with the recommendations of Fergusson et al, BMJ. 2002 Sep 21;325(7365):652-4.

1.4 Study events that occur before surgery. Outcome events that occur after randomization but before surgery will not be counted as events in this study because the study concerns post-surgery events.

1.5 Additional (Secondary) analyses of the primary Aim 1.

1.5.1 Intention to treat and as-treated analyses. In secondary analyses, we will perform both "as treated" and "intention-to-treat" analyses. In the as-treated analysis, patients who received one of the study medications will be included in the statistical analysis in the treatment group corresponding to the treatment that they actually received. In the "intention-to-treat", patients will be included in the statistical analysis in the treatment group corresponding to the treatment to which they were randomized. The intention to treat analysis will include all randomized patients with a few exceptions (see sections 1.3 or 1.4 above). These analyses will be conducted in a manner similar to the per-protocol analysis, but including different patients and different follow-up time.

1.5.2. Analyses aggregating those on either rivaroxaban or warfarin. As an additional secondary analysis, we will also perform a pair-wise comparison of aspirin vs. an aggregate of patients who received either rivaroxaban or warfarin. In this analysis, we will pool the data from those who receive either rivaroxaban or warfarin. This analysis will be based on only those patients eligible for aspirin and either rivaroxaban or warfarin.

1.5.3 Analyses based on different time periods. In an additional secondary analysis, we will compare the treatment groups with respect to risk of events in the first 7 days post-surgery, and in the first month post-surgery.

1.5.4 Analyses adjusting for potential confounding created by exclusion of some patients, loss to follow-up, or switching from randomized treatment. Inevitably there will be some randomized patients who are lost to follow-up at one time or another. These patients will be censored at the time they were lost to follow-up. In addition, as mentioned above, we will censor patients when they switch from the treatment to which they were randomized, and exclude those who do not have surgery or have events before surgery. The missing or excluded data can result in imbalances between

the groups that can confound comparisons. Therefore, in a secondary analysis, we will adjust for these imbalances using weights. Specifically, we will calculate an adjusted Kaplan-Meier estimate using the method described by Xie and Liu (2005, Statistics in Medicine 24:3089:3110). This is an approach that involves weighting each observation by the inverse probability of being in one group (vs. the other group) when calculating the Kaplan-Meier estimates. Candidate variables for weighting will include age, sex, site, date of surgery, and education. Weights will be derived so that, after weighting each participant, the groups will be comparable with respect to the proportion of follow-up in each subgroup defined by the covariates. This will effectively remove confounding due to imbalances between the groups with respect to these measured covariates. These adjusted Kaplan-Meier estimates can be calculated in SAS 9.4.

This approach will result in unbiased estimates if the data are "missing at random" (i.e., missingness may depend on observed patient characteristics but not on the outcome). To address the possibility that the data are "missing not at random" we will perform some sensitivity analyses. One sensitivity analysis will be to perform an intention-to-treat analysis after excluding the sites with the greatest cross-over rates. Another would be to assess impact of various degrees of departure from the missing-at-random assumption on the qualitative conclusions using methods described by Magder LS. (Control Clin Trials. 2003 Aug;24(4):411-21) or by Kim et al (Kim M, Wang C, Xue X. (2019) Stat Med 38:650-659). However, these methods are designed for binary data and will have to be adapted to time-to-event data that we will use as our outcome.

2.0 Primary Aim 2. *To compare the frequency and nature of bleeding complications (major, clinically important, and wound-related bleeding) leading to persistent wound drainage, reoperation, deep infection, or myocardial infarction.*

Using the same methods as described for Aim 1, 6-month probabilities of our primary composite safety endpoint inclusive of bleeding complications by treatment group will be estimated and compared. The primary analysis will be a per-protocol analysis for as described above for Aim 1. Sensitivity analyses for missing outcomes will be performed as described above for Aim 1.

3.0 Primary Aim 3. *To compare patient-reported outcomes (PRO) in patients experiencing primary effectiveness and safety endpoints in order to assess the impact of such events on specific function of the replaced joint as well as general patient well-being.*

3.1 Analysis Plan. The primary patient-reported outcomes will be the HOOS, JR. (hip disability and osteoarthritis outcome score), the KOOS, JR. (Knee injury and osteoarthritis outcome score) and the PROMIS-10 measure of global health. The questions needed to calculate these scores will be asked at each time point (baseline, 1 month, 3 months and 6 months after surgery). These measures will be scored as recommended by the developers. The treatment groups will be compared with respect to the distribution of these scores at each time point. Formal inference regarding the impact of treatment on the changes in these scores will be performed using a general linear model. This will be fit using an unstructured covariance structure to allow a different variance at each time point and different covariances between each pair of time points. The model will include terms representing the mean outcome at each treatment/time/eligibility stratum combination.

In addition, we will compare the treatment groups with respect to specific items used to compute the HOOS, JR and KOOS, JR. For the KOOS, JR, we pre-specify interest in comparing the groups with respect to the following three questions:

1. How severe is knee stiffness after first waking in the morning?
2. What is the degree of difficulty when rising from sitting?
3. What is the degree of difficulty when bending to floor to pick up object?

For the HOOS, JR we pre-specify interest in the following two questions:

1. What is the degree of difficulty when rising from sitting?
2. What is the degree of difficulty when bending to floor to pick up object?

To assess the association between thromboembolic or bleeding complications and patient reported outcomes of function, pain, or quality of life, we will use models similar to those described above. We will add terms to the models representing the experience of a previous thromboembolic or bleeding complication.

As for Aims 1 and 2, the primary analysis will be based on the per-protocol follow-up with secondary analyses based on the intention-to-treat approach and the as-treated approach.

3.2 Scoring the HOOS, JR or KOOS, JR when one or more items in the questionnaire are missing. Patients who complete less than 75% of the HOOS or KOOS questionnaires will be excluded from this analysis. For those who completed 75% or more of the survey questions, missing responses will be imputed using EM (Expectation-Maximization) imputation.

The FORCE study has data on thousands of complete HOOS, JR and KOOS, JR assessments. This information can alternatively be used to develop models for imputing missing items as may be needed. Therefore, unidentified HOOS/KOOS data from our study will be sent to the FORCE team who will perform multiple imputation to result in multiple complete data sets. These data sets will be returned to the statistical coordinating center (UMB) for appropriate analyses of multiple imputation data.

3.3 Addressing the problem of missing PRO data at some follow-up time points. Because the proposed analysis is a likelihood-based analysis, the proposed analyses will be valid if the probability that a patient's PRO is missing at a given time point is at random given observed values of PRO's at other time points. If the probability of missingness is also dependent on other patient characteristics, (e.g., sex, age), these can be included in the model to provide unbiased estimates under the assumption that the probability of missingness is random given observed PRO's and these patient characteristics.

4.0 Secondary Aims Data Analysis

4.1 Secondary Aim 1 Analysis (a): *Analysis of the contribution of "standard of care" methods of anesthesia (general vs regional neuraxial anesthesia) on clinical effectiveness of three different prophylaxis regimens.* To address this aim, we will compare those with general to those with regional anesthesia with respect to risk of the clinical and patient-reported outcomes, overall, and in strata defined by treatment. To assess whether the impact of treatment on outcomes varies by anesthesia type, we will fit longitudinal regression models with interaction terms between treatment and anesthesia type. These models will include random effects for patient and surgeon to account for correlation between repeated measures on the same patient and surgeon. For the binary events in time (e.g., our primary composite outcome for Aim 1), this will be assessed using a Cox regression model with an identity link, censoring patients at the time of loss to follow-up or treatment switch. The interaction terms in this model will represent the difference in the treatment group risk differences between those on general and those on regional anesthesia. The p-values for these terms will provide a measure of the strength of evidence of a difference in treatment effect by anesthesia. We will also adjust for covariates such as age, baseline comorbidities, and surgery type by including them in the model if they appear to confound the relationship between anesthesia and outcomes. Standard errors of estimates in the model will be calculated using a robust variance estimate to account for the clustering within patients and surgeons. We are accounting for clustering by surgeon in the analysis because anesthesia methods may vary by surgeon, so we need to adjust for surgeon.

4.2 Secondary Aim 2 Analysis (b) *Analysis of the relative frequency of thromboembolic events and bleeding complications between hip and knee replacement patients with each of the three regimens.* We will use the methods described above for Aims 1-3 separately for knee and hip patients. Formal assessment of whether event rates or the impact of the treatments differ between those provided knee or hip replacement will be performed using Cox regression with interaction terms between treatment and operation type.

5.0 Power and Precision

5.1 Sample Size. We expect to recruit 20,000 participants. Conservatively assuming 10% of them will not be evaluable, we expect to have data on 18,000 patients. It is estimated that 5% of the patients will be ineligible for aspirin,

2% will be ineligible for rivaroxaban and 1% will be ineligible for Warfarin. It is also estimated (based on the first 6 months of data) that 2.5% of those assigned to aspirin will not be treated with aspirin, 6.4% of those assigned to warfarin will not be treated with warfarin, and 13.6% of those assigned to rivaroxaban will not be treated with rivaroxaban. These patients will be excluded from the primary analysis. Therefore, with a total sample of approximately 20,000, we project that there will be 7239, 7223, and 5389 patients assigned to and treated with aspirin, Rivaroxaban, and Warfarin groups, respectively. We expect to have six-month outcome data on the vast majority of the patients, so we based our precision and power calculations on a binary outcome.

5.2 Precision of Estimates. The primary endpoint is a composite consisting of the occurrence of death from any cause and clinically evident PE or DVT. For an observed endpoint that occurs 1.1% of the time, considering the cross-over rates and conservatively assuming that 10% of those randomized will not have surgery or will be lost to follow-up, the margin of error of our estimates of risk will be 0.27%, 0.30%, and 0.35% for aspirin, rivaroxaban, and warfarin. Clinically significant bleeding is expected to occur in 0.5-1% of patients on aspirin, 4-5% of patients on rivaroxaban, and 1-2% of patients on warfarin. Given those percentages, the margin of error for estimates of bleeding risk will be 0.22%, 0.61%, and 0.41%, respectively.

5.3 Power to confirm non-inferiority. The adoption of a non-inferiority methodology for this trial was predicated on establishing the non-inferiority of aspirin, as compared to either warfarin or rivaroxaban, in preventing death and thromboembolic disease with the assumption that aspirin would very likely result in fewer bleeding complications than either of these two agents. The statistical test of non-inferiority will be based on only those who were medically or logistically eligible for randomization to either of the two groups being compared. Table 1 shows the power to detect non-inferiority for the comparison of aspirin to warfarin with no additional patients randomized to warfarin.

Table 1. Numbers of patients and resulting power and precision in comparing aspirin to warfarin.

	Aspirin	Warfarin
Number Randomized as of May 1, 2023	5132	5389
Number Eligible for both treatments (either medically or due to logistics)	4703	4698
Projected number who took the assigned treatment[1]	4402	3688
Projected number who will have complete follow-up[2]	3962	3319
Projected width of the 95% CI for the difference in risk of primary outcome	0.96 percentage pts	
Power to obtain evidence of non-inferiority based on 0.69% margin of inferiority	80.3%	
Margin of inferiority detectable with 80% power	0.69 percentage pts	

[1]Based on a crossover rate of 21.5% and 6.4% for Warfarin and Aspirin, respectively.
[2]Assuming that 90% of those randomized have surgery, do not withdraw, and have 6-month follow-up information.

Recruitment and randomization. To achieve the total of approximately 18,000 evaluable patients we will recruit approximately 20,000 to accommodate the possibility of 10% loss to follow-up. We will randomize patients with equal probabilities to each of the three regimens using a web-based program provided by Statix. Those sites that are on the restricted randomization plan due to structural barriers will randomize patients using a 1:1 randomization scheme. Following removal of warfarin from the protocol in June 2023, all sites will randomize patients using a 1:1 scheme to either aspirin or rivaroxaban. The web application is available 24/7, password protected, and maintains an audit trail of transactions with time stamp login for users. There will be a separate randomization schedule for each clinical site, stratified according to operation (hip or knee) to ensure balanced intervention groups with respect to site and operation. Within each stratum, assignments will be randomly permuted within repeating blocks of varying size.

Missing Data

A high retention rate of enrolled participants is critical to the internal and external validity of a randomized clinical trial. Patients who are more difficult to locate or are less cooperative in follow-up participation generally have lower social and residential stability, poorer treatment outcomes, and are more likely to experience financial, marital

status, and occupational changes. Many of these same factors are also well known to contribute to differences in health outcomes, health disparities, and healthcare utilization differences. To minimize non-response and loss to follow-up bias, we will rely on independent established third party data collectors who will devote considerable levels of charted effort to follow-up data collection. This approach to centralized data collection will ensure serial efforts to obtain follow-up of research subjects through mail, telephone, electronic communication, and web-enabled online surveys. It will incorporate a 1-800 message, fax and e-mail options for participant convenience, and use postage-paid reply mail service, address forwarding, and multiple efforts in multiple formats to locate patients whose addresses, phone numbers or e-mail become insufficient. Participants will be provided online accounts to complete required surveys. Our centralized data collection center will not have access to randomization assignments in order to minimize bias in data collection. An outcomes assessment committee will blindly review all adverse event reports.
Despite rigorous efforts to minimize missing data or outcome information, inevitably there will be some patients with missing outcome information. We will use the methods described above to mitigate biases due to missing data, or to assess the sensitivity of our results to assumptions about missing data.

Data Management

At monthly intervals Statix, the central data collection agent, will transfer form files electronically to the Data Coordinating Center at the University of Maryland. The Data Coordinating Center 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 at MUSC. Statix will work with the Data Coordinating Center and the Clinical Coordinating Center to achieve complete form submission and correct errors in data items submitted. Delinquent forms and data item corrections will be submitted through the Data Coordinating Center in a process of continual form file updating. The Data Coordinating Center will convert the form files into data analysis files. The biostatistician in the Data Coordinating Center at the University of Maryland, Baltimore, will analyze those data files in consultation with the Executive Oversight Committee 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.

Reporting Plan

Publication and communication of our findings will be made in accordance with the CONSORT statement and its extension for pragmatic clinical trials.[103] In addition to following the standard CONSORT guidelines, our 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 our 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).

3.1.4. Data Sharing

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

With regard to (1) presentations at scientific meetings and publications will target different clinical segments: orthopaedic surgeons, anticoagulation specialists, and hospitalists/general internists. Finding different variations on the themes of study results, we will deliberately present results at different national meetings, taking advantage of the diversity of investigators involved in the study. In addition, 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

and can disseminate via social media. To reach health professionals that are not strong journal readers, we will create short descriptions of the study results for posting on the websites of participating institutions, on Medscape and Doximity medical social networks, and using LinkedIn groups and personal LinkedIn networks.

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 publicly accessible web sites. All software systems developed for preference elicitation will be integrated into public web sites explaining methods, providing demonstrations, and that allow other investigators to adapt displays to improve explanations and/or integrate the displays with additional data. 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. We will integrate our tools into Epic electronic medical records (EMR) software (a widely used system among academic medical centers), using the Epic MyChart Portal and Patient Reported Outcomes toolkit available in the 2014 and 2015 release versions. We work to develop and pilot test appropriate workflows for integrating these Epic tools into routine care and make the software code available to other Epic sites.

3.1.5. Possible Limitations

The most predictable barriers to dissemination and implementation of possible findings that aspirin or warfarin are preferred to rivaroxaban would come from the pharmaceutical industry in light of the substantial investments and potential profits at stake with development of new anticoagulants. Uptake of such findings by patients, physicians, hospitals, and payers will be rapid in anticipation of safety advantages and cost savings.

Should rivaroxaban be found to be substantially superior in efficacy with comparable safety, uptake by patients and medical providers would be anticipated to be rapid based on effectiveness advantages and ease of administration. Surgical providers and hospitals/payers would be slower to adopt new approaches due to concern over relative safety as reflected by increased event rates for bleeding and higher drug and reoperation costs, respectively.

Conceptually, all principal barriers to dissemination have a common foundation: conversion of an area where surgeons have known what to do (e.g. most surgeons had a preferred post op anticoagulant and there were set business processes in place for routine care), to an area where they should practice shared decision making (SDM) and tailor choice of anticoagulant prophylaxis and practice to patients' preferences. Specific barriers will include:

- Acceptance of anticoagulation as an area where patients' preferences should determine therapy. Providers have to set aside their personal experiences and allow patients' preferences to contribute to treatment decisions;
- Cognitive biases. Changes in practices may result in physicians experiencing more memorable and dramatic events (deaths due to PE) than current practices (ie, availability bias);
- Differences in values between patients and physicians. Physicians often place a higher negative value on adverse events than disease related events, despite similar impacts on quality of life. Concerns about malpractice litigation may drive decision-making;
- Acceptance of the methods used to weigh the patient's risk-benefit perspective. Methodological questions about determination of balance between risk and benefit might prevent providers from adopting study results;
- Lack of tools for providers to accurately measure and learn about patients' preferences for anticoagulation in clinical settings. There are currently no good clinical tools to allow a provider to rapidly learn how a patient makes trade-offs between risks and benefits in anticoagulation. Thus it is difficult for providers to tailor care;
- Lack of tools for patients to support SDM on post arthroplasty anticoagulation. While there are several validated decision aids for patients to help decide whether to undergo joint replacement or elect anticoagulation (atrial fibrillation, for example) there are no joint replacement specific tools to elucidate anticoagulation choices, as informed by this study. It may then be difficult for patients to fully participate in anticoagulation decisions;

- Even if good tools are available, the complexity of trade-offs may prevent patients from fully participating in SDM. Patients with lower health literacy may not comprehend trade-off probabilities to share in decisions; and
- Lack of tools in electronic health records to aid in the incorporation of SDM into routine care. Currently there are not good tools to remind providers of SDM contexts in EHRs and to steer them toward SDM practices.

3.2. Study Milestones and Time Line

The trial will include a 9-month start-up phase to include the development of an EDC and operational tools, IRB approval, and initial meetings of study committees (eg. Patient Advisory Board, Steering Committee). The recruitment phase will include the enrollment of approximately 20,000 participants and a 6-month follow up period, and involve the collection of clinical and patient-reported data at enrollment, the perioperative period, and at 1-, 3-, and 6-months post-surgery. This phase will be followed by data analysis and the production of the final report/manuscript.

4. Protection of Human Subjects

4.1. Risks to the Subjects

4.1.1. Human Subjects Involvement and Characteristics

All patients 21 years of age or older who elect to undergo total hip or knee replacement as treatment of end-stage arthritic disease will be eligible for recruitment and enrollment.

The characteristics of the subject population will reflect the characteristics of the general population undergoing total joint replacement; ages will range from mid-30s to mid-80s, and of a general health status that would allow medical clearance for an elective major orthopaedic surgical procedure. We anticipate enrollment of approximately 25,000 patients. Consecutive patients of participating surgeons at a goal of 25 selected institutions under the direction of the field site PI will be recruited and asked to consider enrollment in the study, as noted previously in section 3.1.2a. Recruitment and retention benefits to the subjects include enhanced awareness of prevention, diagnosis, and treatment of standard thromboembolic complications of total joint replacement procedures. Stratified randomization will occur for patients who have a medical contraindication to use of any one or two of the three study prophylaxis regimens for venous thromboembolism employed in the trial as well as for patients at those sites using a restricted randomization scheme due to fixed structural barriers. Exclusion criteria include a preoperative need for chronic anticoagulation other than with antiplatelet medications, a known condition of thrombophilia proven by diagnostic laboratory testing, or any of the criteria previously stipulated in section 3.1.2 (c). No prisoners or other vulnerable patient populations will be included in the study.

It is anticipated that gender of the study participants will reflect that of the general population with arthritic disease, having a slight predilection for women over men by approximately 55% to 45%. Racial and ethnic diversity will reflect the location and socioeconomic nature of the participating sites, a majority of which are urban academic health centers. This fact ensures the quality of the clinical trial infrastructure as well as a balance of urban and rural locations that will preferentially include under-represented racial and ethnic minorities served by these safety net institutions.

A concealed centralized randomization schedule will provide assignment to one of the prophylaxis regimens, as specified in section 3.1.2b, in randomly varying block sizes of 3, 6, and 9 developed separately for each clinical site and stratified according to type of surgery (hip or knee replacement).

Targeted/Planned Enrollment Table

Source of these data is the 2012 National Inpatient Sample for total hip and knee replacement procedures performed in the United States. The prevalence of TKA is roughly 2x that of THA in the United States, so these tables are weighted in such a way that TKA is expected to contribute twice as many patients as THA to the aggregate sample for PEPPER. The relative racial/ethnic/gender data are applied for each procedure in the joint specific table in a ratio of 1:1 for TKA:THA and then added together in the third table to provide overall projections for the study.

Total Planned Enrollment: 20,000

TOTAL HIP REPLACEMENT (1/3 of total 20,000 sample)

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	8	10	18
Asian	19	31	50
Black/African American	180	240	420
Hawaiian/Pacific Islander			
White	2746	3299	6046
Multirace	64	70	134
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	86	100	186
Non-Hispanic	2930	3550	6480

TOTAL KNEE REPLACEMENT (2/3 of total 20,000 sample)

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	21	38	59
Asian	50	117	166
Black/African American	246	742	987
Hawaiian/Pacific Islander			
White	4496	7320	11816
Multirace	104	200	304
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	240	447	687
Non-Hispanic	4678	7969	12646

AGGREGATE SAMPLE – THA and TKA for PEPPER for 20,000

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	29	48	77
Asian	53	148	217
Black/African American	426	982	1407
Hawaiian/Pacific Islander			
White	7242	10619	17862
Multirace	168	270	438
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	326	547	874
Non-Hispanic	7608	11518	19126

These data from the NIS match very closely with the corresponding data below from the FORCE total joint replacement registry, with whom we will closely work to analyze patient reported functional outcomes as baseline information to compare with the information collected in the PEPPER trial.

Racial Categories FORCE Registry	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0.58%	0.38%	0%	0%	0.96%
Asian	0.60%	0.38%	0%	0%	0.98%
Native Hawaiian or Other Pacific Islander	0%	0%	0%	0%	0%
Black or African American	3.90%	2.60%	0%	0%	6.50%
White	52.82%	35.22%	1.16%	0.78%	89.98%
More than one race	0.78%	0.54%	0.16%	0.10%	1.58%
	58.68%	39.12%	1.32%	0.88%	100.00%

(Courtesy, Patricia Franklin, MD)

4.1.2. Sources of Materials

Blinded and coded patient information will be obtained at each field site from the hospital chart, specific data collection forms unique to the proposed study, and routine clinic visits in the outpatient record following operation. No tissue specimens or other matter will be removed from the study subject for purposes of the proposed investigation.

Data will be obtained directly from any diagnostic tests performed to establish the presence of pulmonary embolism, symptomatic deep venous thrombosis, or any site of suspected substantial occult bleeding. Individually identifiable private patient information will only be available at the respective field sites at the time of original data collection. Confidentiality of patient identifiers will be protected except as required by law or for regulatory purpose. Thereafter, all data will be entered into web-based databases in coded form, maintained at the respective individual field sites, and securely stored in the central data management center and web-based repository in aggregate. All patient identification will be removed from data at the field site before aggregate reporting.

4.1.3. Potential Risks

Risks to human subjects 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. There are no experimental drugs or treatment regimens involved in this trial, and so there are no risks associated with any experimental interventions. Likewise, there are no other special risks that are unique to this trial. There are risks associated with randomization since patients will be assigned to a treatment group by chance. One treatment group may prove to be more or less effective or to have more or fewer side effects than the other study treatments or other available treatments. However, each of the three regimens in this trial is commonly used in “standard of care” practice following hip and knee replacement surgery and each has been approved by the FDA and expert guideline groups for use in this manner to prevent venous thromboembolism.

Each of the anticoagulants carries a risk of bleeding, reoperation to evacuate a hematoma from the incision, and secondary infection of the hematoma. 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. Pneumatic compression stockings or foot pumps may be annoying or uncomfortable while wearing them in the hospital. The estimated likelihood of the risks of pulmonary embolism and re-operation for bleeding are as follows:

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%)

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. 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.

Confidentiality Risks

All patient data will be coded and concealed for patient identity at the clinical site in which the patient is enrolled in the trial. Upon initial enrollment, each patient's identity will be concealed by assignment of a numeric identifier that will be contained in the master data file as developed by Statix, as the centralized data collection agent. The data coordinating center, in preparation of the DSMB reports, and the executive oversight committee will have access to unblinded data, but patient identities will remain concealed throughout the trial.

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 (e.g., 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). All participants in DSMB meetings will be required to sign a confidentiality statement at the start of every meeting. All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Electronic versions of data and DSMB material will be stored on secure computers with password protection. Paper copies of forms and reports will be kept in locked filing cabinets with access restricted to a small number of Data Coordinating Center staff members. Access to data will be on a strictly need-to-know basis.

4.2. Adequacy of Protection Against Risks

4.2.1. Recruitment and Informed Consent

Patients will be recruited to the study at each site under approval of a centralized Institutional Review Board at MUSC, or local IRB approval of a modified document to meet local requirements; informed consent will be obtained at each local site prior to central randomization in person or remotely. A common template for the informed consent document will be created centrally 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 either remotely or in the outpatient setting either at the time of the decision to schedule a surgical procedure or at the time of preadmission testing in the weeks prior to the anticipated procedure. 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. A signed consent form will be obtained from each participant at the beginning of recruitment, which will enable the study to collect baseline data and randomize patients. 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.

4.2.2. Protections Against Risk

The clinical and medical risks to human subjects involved in the trial are the same as those undergoing elective hip or knee replacement and receiving standard of care prophylaxis for venous thromboembolic disease. Clinical site directors will assess their patients who experience adverse events or SAEs to assure that they receive the best possible care consistent with contemporary standards of care.

4.3. Potential Benefits of the Proposed Research to Human Subjects

Subjects involved in the proposed trial would potentially benefit from an increased knowledge base relative to the decision regarding anticoagulation type and duration as well as an increased level of vigilance afforded patients with respect to awareness, prevention, diagnosis, and treatment of thromboembolic complications of total joint replacement. There are no risks involved in the study other than those encountered during standard of care prophylaxis for thromboembolism after total joint replacement; each of the three regimens to which patients will be randomized constitutes standard of care in various communities and all have been approved by the FDA for use in VTE prophylaxis.

4.4. Importance of the Knowledge to be Gained

The knowledge to be gained through the proposed study will provide an enhanced level of information about relative risks of VTE prophylaxis to all enrolled patients with a benefit of a more informed decision regarding this therapy. It is possible that results of this trial may establish a new standard of care that provides a balanced approach to prophylaxis of thromboembolic events after total joint replacement that minimizes bleeding complications while optimizing prevention of fatal pulmonary embolism. All future patients undergoing hip or knee replacement would benefit both from an enhanced level of information to aid in decision-making as well as from any established standard of care for VTE prophylaxis.

4.5. Safety Subject and Minimizing Risks (Data and Safety Monitoring Plan)

The DSM plan will be established in accordance with PCORI guidelines. The PI and PCORI leadership will appoint a Data and Safety Monitoring Board (DSMB) to meet every six months, starting with Protocol and Manual of Procedures review late in the start-up period. We anticipate that the expertise represented on the DSMB will include orthopaedic surgery, biostatistics and large sample clinical trials epidemiology, patient-centered outcomes research, and thrombosis and hemostasis (hematology). Some disciplines (e.g., biostatistics and large sample clinical trials epidemiology) may be represented by more than one individual to avoid inability to conduct a conclusive meeting because of scheduling conflicts. An odd number of members is desired to assure that tied votes do not thwart decision making. DSMB members will report to PCORI leadership and to the Principal Investigator, Vincent Pellegrini, M.D. 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 documents, and plans for data and safety monitoring; advising PCORI 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 by commenting on any problems with study conduct, enrollment, sample size and/or data collection. The Principal Investigator with the Data Coordinating Center 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. To maintain the overall Type I error rate below alpha = 0.05, while performing interim monitoring for the primary outcome, we will propose stringent monitoring boundaries for efficacy ($p < 0.001$) and a simple multiple analysis adjustment to the final comparison alpha level because of the small number of interim analyses. We have planned data safety monitoring based on narrative summaries of each serious or unexpected adverse event (SAE) organized through the Outcomes Assessment. On a monthly basis a tabular summary of SAEs and their classification status will be provided to the DSMB and PCORI. Every six months the DSMB and PCORI will receive a report on the clinical trial, presenting SAEs in tabular form as well as outcome information to evaluate safety for the purposes of approving or disapproving continuation of the clinical trial.

Each DSMB member will sign a Conflict of Interest Statement which reports any current affiliation or relationship that could be perceived as a conflict of interest related to the study. This statement will be required prior to the first DSMB meeting and yearly thereafter. At the beginning of every DSMB meeting, the DSMB Chair will ask DSMB members to disclose any new potential conflicts of interest and the DSMB will determine how to handle such potential conflicts. The leadership of PCORI may dismiss a member of the DSMB in the event of unmanageable potential conflict.

5. RESEARCH TEAM AND ENVIRONMENT

The research team is comprised of investigators with complementary skills and perspectives. Drs. Pellegrini, Magaziner, and Magder have worked together planning this project at the U of Maryland since 2009; in April, 2013, Dr. Pellegrini relocated to MUSC. The group has extensive expertise in content (orthopaedic surgery/VTE research) and conduct (clinical trials, epidemiology) domains of the project.

The 16 member ***Steering Committee***, chaired by the PI, is the governing body for the project and will meet in person on a quarterly 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.

The ***Clinical Coordinating Center (CCC)*** will be based at the Medical University of South Carolina and directed by Dr. Pellegrini. The CCC will be responsible for organization of the clinical trial sites, organization of the central IRB residing at MUSC, monitoring of enrollment and overall site performance, reconciliation and payment of all invoices related to the trial, orchestration and arrangement of meetings of site investigators, preparation and submission of regular progress reports to PCORI, and oversight of data analysis and preparation of manuscripts related to the trial.

The ***Data Coordinating Center (DCC)*** will be responsible for receipt and organization of data files from Statix, cleaning and editing of those files for analysis, merging randomization and data files to create unblinded files in support of preparation of reports to the DSMB and the Executive Oversight Committee.

The ***Patient Advisory Board (PAB)*** consists of up to 5 THA and 5 TKA patients (5 men/5 women), two representatives of national patient advocacy groups (National Blood Clot Alliance and North American Thrombosis Forum Patient Advocacy Committee), and a physician expert in study of patient preferences (Lenert). The group is racially and socioeconomically diverse.

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 site reports.

A ***Data and Safety Monitoring Board (DSMB)*** will be formed in accordance with provisions for protection of human research subjects according to MUSC and PCORI guidelines. It will meet twice yearly, or as directed by the SC, OAC, and PCORI staff.

The ***Executive Oversight Committee*** will oversee operational details and ongoing timelines for efficient progress of the study.

Statix is a centralized data collection agency based in Salt Lake City, UT. Statix will serve as the primary centralized data collection agent as well as the randomization agent for the trial.

CTRIC is a research data processing agency based in Baltimore, MD and will assist in data processing and creation of orderly report formats for the DSMB.

6. REPLICATION AND REPRODUCIBILITY OF RESEARCH

Publication of data shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. Research data that documents, supports and validates research findings will be made available after the main findings from the final research data set have been accepted for publication. Such research data will be redacted to prevent the disclosure of personal identifiers. Availability of the data file as part of the plan for dissemination of study results will be announced at scientific sessions where the data are presented and included in the closing acknowledgments of the main study publication(s).

Data Sharing Plan: The participating institutions will follow NIH guidelines concerning the sharing of research

data. As outlined by the NIH and PCORI, the participating institutions will make available to the public the results of this collaboration and any accompanying data that were supported by PCORI. There are no specimens or biological resources for sharing as a result of this planned project.

In the course of this research project, we anticipate generating ranges of estimated complications and adverse events as they relate to the use of VTE prophylaxis in the context of hip and knee replacement. Access to these data and associated recommendations generated under the project will be available for educational, research and non-profit purposes. Such access will be provided using web-based applications, as appropriate and consistent with the data distribution policies of the Medical University of South Carolina and the University of Maryland.

Within nine months of the end of the PEPPER award period, lead investigators will provide PCORI with a well-documented de-identified data file of data items suitable aggregated to protect patients from being individually identified. It will be possible from the data file to replicate substantially the findings of PEPPER publications in the peer-reviewed literature. The lead investigators will make this data file available on a CD with its documentation (variable definitions/code book and citations or images of published work, variable distributions) to any investigator who requests a copy for the cost of reproduction and shipping.

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