






BMJ Open Randomised comparative effectiveness trial of Pulmonary Embolism Prevention after hiP and kneE Replacement (PEPPER): the PEPPER trial protocol

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ABSTRACT

Introduction More than 1 million elective total hip and knee replacements are performed annually in the USA with 2% risk of clinical pulmonary embolism (PE), 0.1%–0.5% fatal PE, and over 1000 deaths. Antithrombotic prophylaxis is standard of care but evidence is limited and conflicting. We will compare effectiveness of three commonly used chemoprophylaxis agents to prevent all-cause mortality (ACM) and clinical venous thromboembolism (VTE) while avoiding bleeding complications.

Methods and analysis Pulmonary Embolism Prevention after HiP and KneE Replacement is a large randomised pragmatic comparative effectiveness trial with non-inferiority design and target enrolment of 20000 patients comparing aspirin (81 mg two times a day), low-intensity warfarin (INR (International Normalized Ratio) target 1.7–2.2) and rivaroxaban (10 mg/day). The primary effectiveness outcome is aggregate of VTE and ACM, primary safety outcome is clinical bleeding complications, and patient-reported outcomes are determined at 1, 3 and 6 months. Primary data analysis is *per protocol*, as preferred for non-inferiority trials, with secondary analyses adherent to *intention-to-treat* principles. All non-fatal outcomes are captured from patient and clinical reports with independent blinded adjudication. Study design and oversight are by a multidisciplinary stakeholder team including a 10-patient advisory board.

Ethics and dissemination The Institutional Review Board of the Medical University of South Carolina provides central regulatory oversight. Patients aged 21 or older undergoing primary or revision hip or knee replacement are block randomised by site and procedure; those on chronic anticoagulation are excluded. Recruitment commenced at 30 North American centres in December 2016. Enrolment currently exceeds 13 500 patients, representing 33% of those eligible at participating sites, and is projected to conclude in July 2024; COVID-19 may force an extension. Results will inform antithrombotic choice by patients and other stakeholders for various risk cohorts, and will be disseminated through academic publications, meeting presentations and communications to advocacy groups and patient participants.

Strengths and limitations of this study

- Large pragmatic randomised comparative effectiveness trial of chemoprophylaxis in preventing venous thromboembolism (VTE) and all-cause mortality after elective total hip and total knee replacement.
- Target enrolment of 20000 patients provides power for concurrent analysis of both effectiveness (VTE) and safety (bleeding) endpoints.
- Non-inferiority design with primary *per protocol* analysis and secondary analysis by *intention-to-treat* principles.
- A 10-patient advisory board contributed to the design and conduct of the trial, emphasising outcomes of importance to patients.
- Interim statistical analysis slated for 50% and 75% of target enrolment with 6-month follow-up and stopping criteria for significant differences in both VTE and bleeding.

Trial registration NCT02810704.

INTRODUCTION

Background and significance

Elective total joint arthroplasty (TJA) of the hip (THA) and knee (TKA) comprise the most commonly performed elective surgeries in the USA, totaling 1.2 million procedures annually. Hospital readmission within 90 days occurs after 10%–15% of elective THA and TKA, and venous thromboembolism (VTE), specifically pulmonary embolism (PE), can be life-threatening.^{1–10} Despite advances in surgical care, fatal PE is reported in 0.1%–0.5% of patients and results in more than 1000 deaths annually following these operations.^{11–13} Post-operative anticoagulation to reduce thrombosis must be tempered by the bleeding risk implicit in orthopaedic procedures.

Accordingly, orthopaedic surgeons typically opt for less intensive, while medical physicians favour more intensive, antithrombotics for TJA patients and clinical guidelines have historically been conflicted. Ideal thromboprophylaxis represents a balance between the risk of fatal PE and the treatment-associated morbidity of bleeding resulting in haematoma or secondary prosthetic infection.^{14 15} Such a critical decision requires definitive evidence about potential benefits and harms, as well as consideration of individual patient preferences about these tradeoffs and risks.

Despite nearly five decades of TJA, there remain substantial evidence gaps concerning VTE prophylaxis.^{16–20} Guidelines from the American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons (AAOS) have historically been at odds, resulting in confusion for both patient and physician.^{21–23} Reconciliation occurred in 2012 with the 2nd AAOS²⁴ and 9th ACCP²⁵ clinical guidelines wherein the ACCP provided greater emphasis on patient concerns about untoward bleeding.²⁶ Both groups agreed that *clinical* VTE was the critical endpoint and acknowledged that insufficient data existed to provide endorsement of any preferred regimen. Few more compelling scenarios demand genuine consideration of outcomes important to patients than an elective operation with a reliable track record of improving quality of life that also carries a small, but real, risk of death and a greater risk of morbid complications that compromise function.

The Pulmonary Embolism Prevention after HiP and KneE Replacement (PEPPER) trial is a large pragmatic randomised clinical trial with non-inferiority design comparing three guideline-approved pharmacological agents popular in North America for prevention of VTE after THA and TKA. Clinical equipoise supports randomisation to three drugs that span the continuum of antithrombotic intensity. Aspirin, 81 mg two times a day, represents low intensity and least costly treatment with minimal perceived bleeding risk and low rates of clinical PE/all-cause mortality (ACM) rates comparable to more intensive therapy.²⁷ Rivaroxaban, 10 mg/day, is a potent oral direct Factor Xa inhibitor, well-studied in randomised controlled trials, with very low VTE rates but higher bleeding risk (3%–5%).^{28–33} Low intensity (INR 1.5–2) warfarin represents a compromise in anticoagulation intensity and has a delayed onset of action; it is historically one of the most commonly used agents having demonstrated effectiveness, low bleeding risk (1%–2%) and low cost.³⁴ Each regimen is endorsed by clinical guidelines of the ACCP, AAOS and American College of Surgeons Surgical Care Improvement Project^{24 25 35} (table 1).

The hypothesis is that aspirin prophylaxis of clinically meaningful VTE and death after THA and TKA *will not be inferior* to low intensity warfarin (INR 2.0) or rivaroxaban, and will result in fewer bleeding events with less reoperation, infection and myocardial infarction, that compromise patient-reported outcomes (PROs) for general well-being and joint-specific function.

Table 1 Clinical event risks for aggregate bleeding and pulmonary embolism associated with the three antithrombotics studied⁵³

Study medication	Risk of reoperation for bleeding	Risk of 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%)

METHODS AND ANALYSIS

Study setting and site selection

The clinical coordinating centre (CCC) originated at the Medical University of South Carolina and transferred to Dartmouth-Hitchcock with relocation of the study PI (Principal Investigator). The data coordinating centre (DCC) resides at University of Maryland. An executive oversight committee (EOC) governs study operations. A patient advisory board (PAB), steering committee (SC), and data and safety monitoring board (DSMB) meet semi-annually (figure 1).

Enrolment occurs at North American THA and TKA referral centres (PEPPERstudy.org). Site requirements are: (1) willingness of individual participating surgeons to randomise eligible patients to all three treatment groups; (2) a minimum of two participating surgeons; (3) institutional experience with clinical trials; (4) existing research infrastructure or commitment to develop one; (5) adequate THA/TKA volume to provide enrolment of 1000 patients over 3 years; and (6) in the USA or Canada.

Primary reasons for site exclusion include: (1) unwillingness to randomise to all three groups; (2) budgeting or contractual limitations and (3) competing or conflicting studies. Institutions exhibiting structural barriers to use of warfarin (no INR monitoring) or rivaroxaban (no copay support) limit patient randomisation to only two treatment groups.

Eligibility

Inclusion criteria

Males and females 21 years of age or older undergoing unilateral elective hip or knee replacement, primary or revision, and medically eligible for randomisation to at least two of the study drugs.

Exclusion criteria

Patients undergoing *bilateral* THA or TKA; previously enrolled in PEPPER; concurrently enrolled in another active interventional VTE prophylaxis trial; or on chronic (longer than prior 6 months) anticoagulation. Patients with documented gastrointestinal, cerebral or other haemorrhage within 3 months; a diagnosis of defective hemostasis and history of spontaneous bleeding requiring transfusion; having an operation involving the eye, ear or central nervous system within 1 month; uncontrolled hypertension (systolic blood pressure (BP) >220 mm Hg or diastolic BP >120 mm Hg); inadequate cognitive

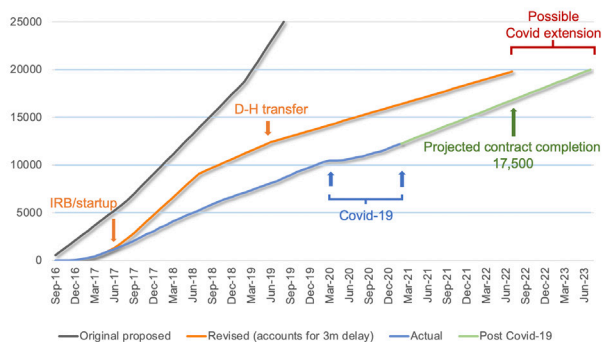


Figure 1 Pulmonary Embolism Prevention after Hip and Knee Replacement trial enrolment progression. Establishment of central IRB finalised 3 months after study contract signed with Patient Centered Outcomes Research Institute in March 2016. Study enrolment commenced in December 2016. Progressively more sites were added during first 12 months of trial; average time for contracting and infrastructure startup to enrolment ranged from 6 to 9 months. Study PI and prime contract transferred home institutions in June 2019. COVID-19 impact suspended elective surgery and research activity in nearly all sites commencing on or following March 2020 with sporadic resumption of research activities by 1 year later. Extension of the trial may be necessary as a result of the negative impact of COVID-19 on elective surgery and clinical research activities in the USA and Canada. IRB, institutional review board.

capacity to complete study assessments, or baseline body weight less than 41 kg (90.4 lbs). Pregnant or breastfeeding women of reproductive potential without a negative pregnancy test on day of surgery, and vulnerable populations including prisoners and institutionalised individuals are ineligible. Premenopausal women of childbearing potential include those not having had bilateral oophorectomy, hysterectomy or tubal ligation. Postmenopausal is defined as no menstrual period for one calendar year.

Patient screening and consent

Study subjects must meet protocol requirements, provide informed consent and agree to be randomised. Consent follows an introduction by the surgeon and an in-person discussion with a trained study team member. Live virtual remote consenting, implemented due to COVID-19 restrictions, and an educational video developed in conjunction with patients have been used.

All patients scheduled for elective THA or TKA are screened and all eligible patients are approached for participation. A patient is considered enrolled when all eligibility criteria are met and the institutional consent form (PEPPERstudy.org) is signed. Surgeon confirmation of eligibility is required prior to randomisation.

Interventions

Aspirin is initiated prior to surgery (162mg po) on the day of operation. Starting postoperative day #1, patients receive 81 mg po two times a day.

Warfarin is initiated prior to surgery on the day of operation. Initial dosing is by body weight: less than 125 lbs—2.5mg; 125–250 lbs—5mg; greater than 250 lbs—7.5mg. The initial dose is repeated on the evening of surgery if the preoperative dose was received before noon. Starting postoperative day #1, patients receive adjusted dose warfarin each evening to achieve a target INR of 2.0 (range 1.7–2.2).^{34 36} Monitoring is per local practice.

Rivaroxaban (10 mg po) is initiated on postoperative day #1, 24 hours after arrival in the recovery room. Starting postoperative day #2, rivaroxaban is administered each evening.

Study medications continue for 30 days in all groups. Continuation of study medication after any primary study endpoint or adverse event is subject to judgement of the treating physician. Data collection continues to complete 6-month follow-up. Patients on preoperative cardiac dose aspirin; (1) continue their regular cardiac dose if randomised to warfarin or rivaroxaban, or (2) change aspirin dosing to conform with PEPPER if randomised to the aspirin group. Pneumatic compression devices are used in all groups per local practice.

Blinding

Study group assignments are shared with the surgeon, clinical team and patient prior to operation. Follow-up data collection, event adjudications and statistical analyses are performed with blinding to treatment group.

Randomisation, allocation, and implementation

Randomisation occurs until the day before scheduled surgery and is available 24/7 via a password protected time-stamped web-based system after baseline database instruments are completed. Random permuted blocks ensure balanced patient assignment to one of three treatment groups by operation and site. A contraindication to one of three regimens will result in 1:1 randomisation to the other two regimens. Following initial trial registration, the protocol was modified to allow limited select sites with structural impediments to use of either warfarin or rivaroxaban to omit that drug and randomise 1:1 to the other two drugs. Eligibility for two study regimens is required for patient participation in the trial.

Aspirin will be excluded from patients with:

1. Known aspirin allergy.
2. Personal history of PE/Deep Vein Thrombosis (DVT).
3. Proven thrombophilia by diagnostic testing, for example, Factor V Leiden.
4. Cancer diagnosis under active treatment.

Rivaroxaban will be excluded from patients:

1. With serum creatinine greater than 2.0mg/dL.
2. Taking medications that inhibit CYP 3A4.

Warfarin will be excluded from patients:

1. With history of warfarin-related necrotising skin lesions.

Patient and public involvement

A multidisciplinary stakeholder team, including a 10-patient advisory board, participated in development of the research question and selection of both interventions and clinical outcomes to ensure consideration of patient priorities and preferences. Following initiation of the trial, the PAB advises on matters of patient recruitment, follow-up contact, adjunct studies, and will be involved in the analysis and interpretation of the final outcomes data. Results will be disseminated to all study participants who expressed interest in the outcomes through their local site of enrolment.

Primary outcomes

Clinical endpoints and functional outcomes are assessed through 6 months. The **primary effectiveness endpoint** is the aggregate of ACM and clinical VTE (PE, DVT), confirmed by imaging and resulting in readmission and/or therapeutic anticoagulation. Only the first or more serious event is counted in each patient. *Deaths* will be classified as cardiovascular, if sudden and otherwise unexplained, or myocardial infarction, stroke, heart failure, arrhythmia or PE. The **primary safety endpoint** is the aggregate of major bleeding, clinically important wound or remote bleeding, persistent wound drainage, reoperation for delayed wound healing or removal of the implant for infection, and myocardial infarction. *Major bleeding* is that which is fatal, occurs in a critical organ or space (intracranial, epidural, intraspinal, retroperitoneal, intraocular, pericardial), results in reoperation or remote clinically overt bleeding with a fall in haemoglobin of 20 g/L, managed with transfusion of two or more units of blood, or prolongs hospital stay.^{37 38} *Non-major clinically important wound-related bleeding* is persistent drainage beyond 5 days postoperatively or delayed healing that requires wound care after 2 weeks or staple removal. There is no VTE screening; clinical DVT is diagnosed by loss of compressibility on ultrasound³⁹ or a filling defect on contrast venography. PE is diagnosed by contrast-enhanced chest CT,⁴⁰ ventilation-perfusion scanning or pulmonary angiography. Myocardial infarction is diagnosed by laboratory-defined elevation in troponin and/or EKG changes. The **primary functional endpoint** is joint-specific PRO (hip (Hip Disability and Osteoarthritis Outcome Score (HOOS))⁴¹ or knee (Knee Disability and Osteoarthritis Outcome Score (KOOS))⁴² disability and osteoarthritis scores) and general well-being (PROMIS-10 global health)⁴³ at 1, 3 and 6 months.

Subgroup analyses

Comparison of event rates in treatment subgroups defined by: (1) 'standard of care' anaesthesia methods (general vs regional/neuraxial)^{27 44 45} and (2) THA and TKA. Discordant patient (PAB) and physician (SC) anticoagulation preferences and risk tolerances will be reported.

Sample size determination

Sample size was designed to provide power to concurrently study both thrombosis and bleeding as surrogates for anticoagulant effectiveness and safety. Only clinically apparent events were considered. Conservative assumptions for fatal PE (0.1%), clinical VTE (2%) and clinical bleeding (1%–5%) span the range of the three studied agents. Projections assumed enrolment of 22% of eligible patients reaching 25 000 at 25 centres over 3 years. To date, enrolment of 34% of eligible patients has been achieved across all active sites.

Based on actual observed study event rates, the sample size was revised downward to 20 000 participants. Conservatively assuming 10% of them will not be evaluable, we expect to have data on 18 000 patients. Based on experience thus far, it is estimated that 7% of the patients will be ineligible for aspirin, 2.4% will be ineligible for rivaroxaban and 0.1% will be ineligible for warfarin. It is also estimated (based on the first 6 months of data and accounting for restricted randomisation at some sites) that 6.1% of those assigned to aspirin will not be treated with aspirin, 20% of those assigned to warfarin will not be treated with warfarin and 26.2% of those assigned to rivaroxaban will not be treated with rivaroxaban. These patients will be excluded from the primary 'per protocol' analysis after they switch medications. With a total sample of 18 000, considering the use of restricted randomisation at 10 sites and the 1–1 randomisation, we project that for the per protocol analysis there will be 6050, 4306 and 4789 patients assigned to and treated in the aspirin, rivaroxaban and warfarin groups, respectively.

Precision

The primary endpoint is a composite consisting of the occurrence of death from any cause and clinically evident PE or DVT. We conservatively anticipate a primary endpoint in 2.5% of patients. For an observed endpoint that occurs 2.5% of the time, the two-sided 95% CI for the true proportion will be approximately (2.03% to 2.97%) for the rivaroxaban group and slightly narrower for the other two groups. Clinically significant bleeding is expected to occur in 4%–5% of patients on rivaroxaban, 1%–2% of patients on low-dose warfarin, and 0.5%–1% of patients on aspirin. For an observed proportion of 5%, the two-sided 95% CI for the true proportion will be approximately (4.33% to 5.67%); for an observed proportion of 0.5%, the CI will be approximately (0.28% to 0.72%). If the rate of events is equal to 2.5% in both the aspirin group and the rivaroxaban group, the expected 95% CI for the risk difference will be (–0.65% to +0.65%).

Power

The adoption of a non-inferiority methodology for this trial was predicated on establishing the non-inferiority of aspirin, as compared with 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 of aspirin relative to rivaroxaban will be based on only patients who were medically eligible for randomisation to either of those two groups. Allowing for 10% of patients with missing follow-up, accounting for those not treated with the study medication to which they were assigned, and excluding those who were at sites that did not randomise to rivaroxaban, we project that there will be 3942 patients in the rivaroxaban group and 4909 patients in the aspirin group. If the true risk of a primary endpoint is 2.5% for patients given either aspirin or rivaroxaban, the study will retain approximately 80% power to show that aspirin is not inferior to rivaroxaban by more than 0.94 percentage points, or a 37.6% increase in the risk of an event, using a standard large-sample one-sided test and a 0.025 significance level. Equivalently, the probability will be 80% that a two-sided 95% CI for the risk difference between aspirin minus the risk with rivaroxaban will have upper limit less than 0.94%. For the comparison of aspirin and Warfarin, we project that we will have 4395 and 5058 comparable patients in the two groups and that we will have 83% power to reject inferiority of aspirin to warfarin by the same 0.94% margin. For the additional comparison of warfarin and rivaroxaban, which was not the basis for selecting the non-inferiority methodology, we project to have 3509 and 3798 patients in the two groups, respectively, providing 80% power to reject inferiority by a margin of 1.03 percentage points.

Using these assumptions, the margin of inferiority (table 2) that will be detectable given the different event rates from a final sample of 20 000 randomised patients is as follows.

For example, in the riva/aspirin comparison, if the true event rate is 3.0% (in both groups), there will be 80% power to reject inferiority by a margin of 1.023 percentage points (or equivalently, by a factor of 1.341). Greater actual event rates provide a smaller relative margin of non-inferiority and a slightly larger absolute percentage point difference of non-inferiority.

Data collection and participant follow-up

All events are audited locally at hospital discharge, and collected centrally by a blinded independent third party data service (Statix, LLC; Salt Lake City, Utah, USA) at 4 weeks (+10 days), 3 months (± 10 days), and 6 months (+3 months/ -1 month) after operation (table 3). Serial

efforts are made to obtain follow-up by mail, email, telephone and web-enabled online surveys. Statix personnel interview patients about adverse events and collect PROs (HOOS, KOOS, PROMIS-10), available at PEPPER-study.org. Patients without central 6-month follow-up are contacted by site coordinators to complete surveys. Medical records from all treatment facilities are collected by local PEPPER staff for endpoint or adverse events (identified by patient-report or ad hoc discovery), and patients lacking 6-month follow-up. All endpoints are adjudicated by two independent physicians (Outcomes Assessment Committee) blinded to study groups.

Data management/monitoring

Biweekly electronic enrolment and randomisation data are archived, edited and reported as blinded files by the DCC to the CCC and EOC. Statix follow-up data are downloaded quarterly. Deaths are monitored in real time. Batched adverse event triage and adjudication occurs semiannually on patients who have passed the 6-month window. A distinct unblinded DCC statistician analyses and prepares DSMB reports every 6 months. Site data collection and processes are audited annually by the study team.

No outcome or endpoint data are exchanged with clinical sites. Enrolment and follow-up figures are made available in a secure password protected section of the trial website.

Statistical methods/data analysis plan (at PEPPERstudy.org)

The trial's conceptual basis is to establish non-inferiority of aspirin, compared with warfarin or rivaroxaban, in preventing VTE and death. It is anticipated that aspirin would result in fewer bleeding complications than either of the other treatments. While the ITT principle is the basis for analysis of superiority trials, ITT is biased towards finding non-inferiority because protocol violations and cross-overs tend to diminish differences between groups.^{46 47} Therefore, *the primary analysis of non-inferiority will be a per protocol analysis of patients receiving the medication to which they were randomised. If a patient switches treatments, s/he will be included in a per protocol analysis only up until the time the treatment changed.*⁴⁶ In this pragmatic trial the goal is to estimate event risks in a real world setting. This per protocol analysis is not a

Table 2 Pulmonary Embolism Prevention after HiP and KneE Replacement inferiority margins with observed event rates for both aspirin comparison

Event rate (%)	Rivaroxaban/aspirin comparison		Warfarin/aspirin comparison	
	Absolute difference (%)	Relative difference	Absolute difference (%)	Relative difference
2.5	0.935	1.374	0.902	1.361
3.0	1.023	1.341	0.984	1.328
3.5	1.102	1.315	1.060	1.303

*StatisticalAnalysisPlan,ThePEPPERTrial.atwww.PEPPERstudy.org

Table 3 Timeline for baseline and longitudinal data collection for patients enrolled in Pulmonary Embolism Prevention after Hip and Knee Replacement

	Screening	Baseline (-3 months to -1 day)	Randomisation (surgeon confirmation to -1 day)	Surgery (day 0)	Postoperative (day 1)	Hospital discharge	4-week FU (+10 days)	3-month FU (±10 days)	6-month FU (±1 month)
Prescreen 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
Randomisation			X						
Urine pregnancy test				X*					
Study Drug Administration (aspirin and warfarin arms)				X (ongoing for 30 days)	X	X	X		
Study Drug Administration (rivaroxaban arm)					X (ongoing for 30 days)				
Perioperative form					X	X			
AE(Adverse Events)/SAS(Serious Adverse Events) monitoring			X	X	X	X	X	X	X

*Urine pregnancy test done as standard of care and results will be reviewed for research purposes.

AE, Adverse Events; FU, follow-up; HOOS, Hip Disability and Osteoarthritis Outcome Score; KOOS, Knee Disability and Osteoarthritis Outcome Score; SAE, Serious Adverse Events.

traditional one, which would exclude all patients who do not fully adhere to their medication assignment.

In secondary analyses, we will also perform intention-to-treat (ITT) analysis and ‘as-treated’ analyses. In the ITT analysis, patients will be included in the analysis in the group to which they were randomised and only be censored when they are lost to follow-up. In the ‘as-treated’ analysis, patients will be included in the group based on the study medication they actually received. This approach includes crossover patients and provides more precise estimates of what actually happened to patients who took the study medications, but will need to be interpreted with caution as it has more potential for a lack of group representativeness.

For each pairwise comparison of treatment groups, the statistical test of non-inferiority will be based on analysis of only patients eligible for randomisation to either of the two groups compared and only from sites when patients could have been randomised to either of the two treatments being compared. Defining the non-inferiority margin is critical; it should be no more than the presumed entire effect of the active comparator.⁴⁸ Projecting a primary endpoint (VTE plus ACM) in 2.5%, a conservative non-inferiority margin for aspirin was defined as one percentage point or an effect no more than 40% greater than the comparator effect. With an actual primary endpoint in 1.5%, the study will retain 80% power to show aspirin is not inferior to rivaroxaban by more than 0.73 percentage points (49%) using a standard large-sample one-sided test ($p=0.025$). For comparison of aspirin and warfarin, 80% power is retained to reject inferiority by a similar margin (0.71 percentage points; 47%). With 20 000 patients, smaller actual event rates provide greater relative margins and slightly smaller

absolute percentage point differences of non-inferiority (table 4).

A composite of primary effectiveness *and* safety endpoints will also be evaluated. This assessment of ‘net clinical benefit’ will compare a combined measure, the number of patients with either a primary effectiveness (DVT/PE plus ACM) or safety (aggregate bleeding events) endpoint between groups.⁴⁹

Interim analyses

We do not anticipate stopping the trial early based on interim analyses of non-inferiority since evidence for inferiority with respect to *both* safety and efficacy should be present to end randomisation. The DSMB can recommend stopping randomisation to any medication (or modifying its dose) at any time based on safety concerns; prespecified outcomes leading to early stopping would be significant differences in (1) ACM or (2) both thrombotic and bleeding events. To preserve final $p=0.05$ level type-1 error rates for any specific comparison, the DSMB will use p values of 0.002 at interim analyses of 50% and 75% of the sample to define statistical significance consistent with the Haybittle-Peto approach.^{50 51} The DSMB should consider stopping randomisation to a particular treatment if, at any interim analysis, (1) the two-sided p value comparing one treatment to another with respect to ACM is lower than the corresponding threshold or (2) the two-sided p values comparing one treatment to another with respect to *both clinical thrombosis (DVT or PE) AND major bleeding events* is lower than the corresponding threshold.

Table 4 Statistical power

Number of patients randomised	Event rate (%)	Rivaroxaban/aspirin comparison		Warfarin/aspirin comparison	
		Absolute difference with 80% power to rule out (%)	Relative difference with 80% power to rule out	Absolute difference with 80% power to rule out (%)	Relative difference with 80% power to rule out
20 000	0.75	0.52	1.69	0.50	1.67
	1.00	0.60	1.60	0.58	1.58
	1.25	0.68	1.54	0.65	1.52
	1.50	0.73	1.49	0.71	1.47
18 000	0.75	0.55	1.73	0.53	1.70
	1.00	0.63	1.63	0.61	1.61
	1.25	0.71	1.56	0.68	1.54
	1.50	0.77	1.52	0.74	1.50
16 000	0.75	0.58	1.77	0.56	1.75
	1.00	0.67	1.67	0.65	1.65
	1.25	0.75	1.60	0.72	1.58
	1.50	0.82	1.55	0.79	1.53

Absolute and relative margins of difference with 80% power to exclude with specified sample sizes and event rates.

ETHICS AND DISSEMINATION

Institutional Review Board approval

The institutional review board (IRB) for human subjects research at the Medical University of South Carolina approved the study protocol and consent forms on 19 April 2016 (Pro00053742) and serves as the central IRB (cIRB). Of the 31 approved sites in North America, 27 relied on the cIRB; 2 USA and 2 Canadian sites are governed by local IRBs with guidance from the cIRB. Annual cIRB review was completed on 16 February 2021. Study documents and protocol modifications are available at PEPPERstudy.com. The study is funded by PCORI, and this report (Protocol version May 28, 2020) follows Standard Protocol Items: Recommendations for Interventional Trials guidelines.

Safety monitoring

An independent 5-member DSMB (two orthopaedic surgeons (one as chair), one haematologist, one cardiologist and one biostatistician) oversees study participant safety and overall trial conduct (charter at PEPPERstudy.org). Each member has signed, and regularly renews, a conflict of interest statement reporting relevant relationships. The DSMB reviews research protocol and informed consent documents; ensures data quality and study participant safety; reviews interim analyses; recommends early trial termination, modification or continuation; and advises the PI of any patient safety concerns or trial conduct recommendations. Study closure will be considered in consultation with the PI after outcome data and analyses are complete.

Dissemination policy

Publication of outcomes data will occur at project conclusion, consistent with normal scientific practices. Redacted data will be made available after main research findings are accepted for publication. Participating institutions will follow NIH data sharing guidelines. Ranges of adverse events related to VTE prophylaxis and associated recommendations will be provided using web-based applications consistent with policies of Dartmouth-Hitchcock Medical Center and the Trustees of Dartmouth College.

Trial status

As of 1 December 2021, 13663 patients have been enrolled, representing 33% of eligible patients at participating sites. With actual mortality of 0.3% and no more than 5% loss to follow-up, a sample size of 20000 is projected by July 2024. Delays in central IRB implementation and the COVID-19 pandemic may extend enrolment beyond 6 years (figure 1). Experience finds ineligibility of 7% of patients for aspirin, 2.4% for rivaroxaban, and 0.1% for warfarin (figure 2).

DISCUSSION

PEPPER is the largest randomised trial of VTE prophylaxis after total joint replacement. It will provide much

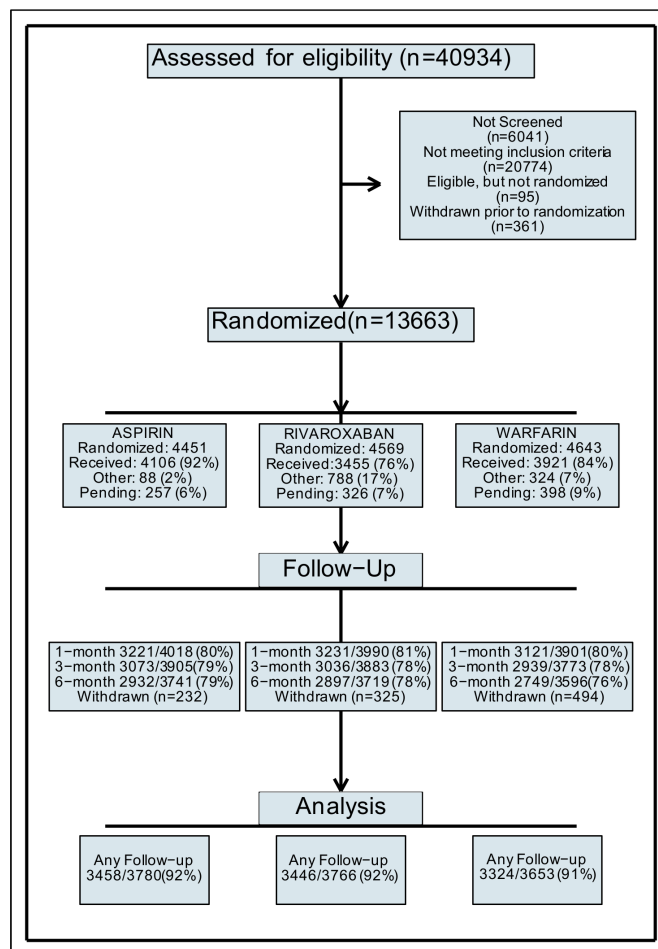


Figure 2 Pulmonary Embolism Prevention after Hip and KneE Replacement (PEPPER) trial Consolidated Standards of Reporting Trials (CONSORT) diagram. As of the end of November 2021, 13663 patients were randomised into PEPPER. More than 33% of all eligible patients undergoing total hip or knee replacement at participating centres agreed to participate in the trial. Approximately 80% of patients provided follow-up at 6 months through a centralised mechanism, as depicted in the CONSORT diagram. Local site efforts contribute to aggregate 6-month follow-up of greater than 95%.

needed unbiased data regarding relative safety and efficacy of aspirin, rivaroxaban and warfarin and facilitate individualised prophylaxis for patients with various risk profiles. Similar actual event rates for clinically important effectiveness and safety endpoints will provide sufficient power for assessment of both thrombosis prevention and bleeding avoidance. As a large pragmatic trial, PEPPER reflects real world challenges related to drug cost, monitoring and adherence and their impact on outcomes. Since 25% of readmissions go to facilities other than that of the index procedure, patient event reporting will increase data on events of importance to patients,⁵² and a PAB ensures that endpoints and results interpretation will consider patient preferences. The PEPPER trial offers the prospect of objectively informing this critical patient care decision for more than 1 million individuals undergoing

joint replacement annually in the USA at a time when rapid transition to expedited discharge and increasing financial constraints from bundled payments make the window of opportunity to conduct this important trial now or never.

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