COVET

Study Protocol

Amendment 3

Comparison of Oral anticoagulants for extended VEnous Thromboembolism (COVET)
NCT03196349

Original Protocol Version Date: May 15, 2017

Amendment 1 Version Date: October 10, 2017

Amendment 2 Version Date: December 08, 2017

Amendment 3 Version Date: September 21, 2018

Principal Investigator: Thomas Ortel, MD

Co-Principal Investigator: Lana Castellucci, MD

Co-Principal Investigator: David Garcia, MD

Statistical Investigator: Kevin Anstrom, PhD

Funded by Patient Centered Outcomes Research Institute (PCORI) NOACs 1511-33599

authorization from DCRI.

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date
Version 1	15May2017
Amendment 1	10October2017
Amendment 2	08December2017
Amendment 3	21Sep2018

PROTOCOL SYNOPSIS

Protocol Title	Comparison of Oral anticoagulants for extended VEnous Thromboembolism (COVET)
Main Criteria for Inclusion	Age 18 years and older; confirmed acute, symptomatic first unprovoked lower extremity proximal DVT and/or PE, completed initial course of oral anticoagulation therapy for 3-12 months and recommended for continued anticoagulation, under the care of a healthcare provider for treatment of VTE during study participation
Study Objectives	**Primary Safety Objectives:** • Determine if apixaban is superior to warfarin in the reduction of clinically relevant bleeding. • Determine if rivaroxaban is superior to warfarin in the reduction of clinically relevant bleeding **Primary Efficacy Objectives:** • Determine if apixaban is non-inferior to warfarin in the prevention of recurrent venous thromboembolism. • Determine if rivaroxaban is non-inferior to warfarin in the prevention of recurrent venous thromboembolism. **Exploratory Objective:** • An exploratory descriptive comparison of apixaban versus rivaroxaban for the prevention of clinically relevant bleeding and recurrent VTEs as a secondary objective.
Study Design	Randomized, open label, active comparator
Treatment Regimen	Warfarin, apixaban, or rivaroxaban
Duration of Study Participation	12 months
Number of Patients	Approximately 3000
Number of Sites	Approximately 60 sites in the US and Canada
Primary Efficacy Endpoint	Recurrent venous thromboembolism
Primary Safety Endpoint	Clinically relevant bleeding
Interim Analyses	There will be no formal interim analyses for the primary efficacy or safety endpoints. The Data and Safety Monitoring Board will meet regularly to review patient safety and overall study conduct.

TABLE OF CONTENTS

ABBREVIATIONS

ACTS	Anti-coagulation Treatment Scale
AE	Adverse Event
CEC	Clinical Events Committee
CI	Confidence Interval
CRCL	Creatinine Clearance
CRNMB	Clinically Relevant Non Major Bleeding
DCRI	Duke Clinical Research Institute
DL	Deciliter
DOACs	Direct Oral Anticoagulants
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
EQ-5D-5L	EuroQoL-5D-5L
FDA	Food and Drug Administration
HR	Hazard Ratio
ICF	Informed Consent Form
INR	International Normalized Ratio
IPW	Inverse Probability Weighted
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
MB	Major Bleeding
NBCA	National Blood Clot Alliance
PCORI	Patient Centered Outcomes Research Institute
PE	Pulmonary Embolism
PI	Principal Investigator
RCT	Randomized Clinical Trial
RR	Relative Risk
SAC	Study Advisory Committee
VTE	Venous Thromboembolism
VKA	Vitamin K Antagonists

V/Q	Ventilation Perfusion

1. INTRODUCTION

1.1 Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common, potentially fatal, yet treatable condition and is the third leading cause of mortality by cardiovascular disease (White 2003; Heit 2006; Kyrle 2004). It represents an important health care issue due to its high rate of hospital admission and potential reduction in functional status of survivors due to VTE related complications such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. Up to 5% of the population will experience VTE in their lifetime and the majority of these events will be unprovoked (White 2003). VTE is predominantly a disease of the elderly with incidence rates increasing exponentially with age for both men and women (White 2003; Heit 2006; Kyrle 2004). The standard therapy for patients with VTE is anticoagulation for 3-6 months; the most common oral anticoagulants used are vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) (Kearon 2012).

After completing 3-12 months of anticoagulation, patients, clinicians and policy makers are faced with the crucial decision of whether or not to continue anticoagulation lifelong. In patients with unprovoked VTE, the risk of recurrent VTE is substantial, reaching 5%-10.8% in the first year after stopping 3-6 months of VKA, 5% in the subsequent year (Agnelli 2001) and 2-3% per year thereafter (Agnelli 2001; Prandoni 1996; Kearon 1999; Schulman 1995; Research Committee 1992), with a case-fatality rate for recurrent VTE of 3.6% (Carrier 2010). Since up to 75% of unprovoked VTE patients would benefit from continuing anticoagulants lifelong (Rodger 2008), current guidelines recommend indefinite anticoagulant therapy for patients in this category (Kearon 2016). With this decision, the next crucial question becomes which anticoagulant to choose. Treatment with VKA presents many challenges including drug and food interactions, and a narrow therapeutic window requiring regular laboratory monitoring; these can be particularly burdensome for elderly patients and those with many co-morbidities who require intensive monitoring, frequent trips to the laboratory and subsequent dosing changes. DOACs are simpler to use as they have more predictable pharmacokinetic properties (Vilchez 2014) and do not require monitoring. A major limitation of DOACs however, is the lack of comparison trials demonstrating a favorable benefit-to-risk ratio of DOACs over VKAs for long term anticoagulation in VTE patients. This gap in the evidence highlights the decisional dilemma patients, clinicians, and stakeholders are faced with when choosing which anticoagulant to use for long-term prevention of recurrent VTE.

1.2 Preclinical Findings

The information on comparative effectiveness between rivaroxaban or apixaban and warfarin (target INR 2-3) is derived from industry-sponsored trials for treatment of acute VTE (Einstein Investigators 2010; Buller 2012; Agnelli 2013a). The duration of treatment in these trials was defined as the initial 3-12 months of anticoagulation after diagnosis of acute VTE. Einstein-DVT included nearly 3500 patients with proximal DVT and no symptomatic PE (Einstein Investigators 2010). Rivaroxaban was shown to be non-inferior to warfarin for the primary efficacy outcome of recurrent VTE with an event rate of 2.1% in the rivaroxaban arm and 3.0% in the warfarin arm (hazard ratio (HR), 0.68; 95% confidence interval (CI), 0.44 to 1.04). The

primary safety outcome was clinically-relevant bleeding, a composite of major bleeding or clinically-relevant non-major bleeding events, occurred in 8.1% of patients in each group. Einstein-PE enrolled 4800 patients with acute PE with or without DVT (Buller 2012). The primary efficacy and safety outcomes were identical to the Einstein-DVT trial. Rivaroxaban was similarly shown to be non-inferior to warfarin for the primary efficacy outcome with 2.1% of patients in the rivaroxaban arm versus 1.8% in the warfarin having recurrent events (HR 1.12; 95% CI, 0.75 to 1.68). Bleeding occurred in 10.3% of patients in the rivaroxaban group and 11.4% in the warfarin group. The Amplify RCT compared apixaban to warfarin in 5400 patients with acute VTE (Agnelli 2013a). The primary efficacy outcome of recurrent VTE occurred in 2.3% of patients in the apixaban group and 2.7% in the warfarin group (Relative risk (RR), 0.84; 95% CI, 0.60 to 1.18), demonstrating non-inferiority of apixaban to warfarin. The primary safety outcome of major bleeding occurred in 0.6% of patients in the apixaban group compared to 1.8% in the warfarin group, meeting pre-specified criteria for superiority.

1.3 Long-term prevention of recurrent VTE (after treatment of acute event)

Rivaroxaban and apixaban have each been compared to placebo for extended anticoagulation in patients who had completed 6 to 12 months of anticoagulation for the index VTE event (Einstein Investigators 2010; Agnelli 2013b). In both trials, extended anticoagulation treatment was for 12 months duration, the primary efficacy outcome was recurrent VTE and the primary safety outcome was major bleeding. In the Einstein-EXT RCT, 1200 patients were included and rivaroxaban was superior to placebo for preventing recurrent VTE (1.3% for rivaroxaban and 7.1% for placebo; HR, 0.18; 95% CI, 0.09 to 0.39) (cf. Table 1). Major bleeding events occurred in 0.7% of patients in the rivaroxaban group compared to no bleeding events in those on placebo. Clinically relevant bleeding (MB or CRNMB) events occurred in 6.0% of patients receiving rivaroxaban and 1.2% of those on placebo (cf. Table 2). The Amplify-EXT RCT compared two doses of apixaban (5 mg and 2.5 mg, twice daily) to placebo (Agnelli 2013b). Both doses of apixaban were superior to placebo in this trial of 2500 patients. The rates of recurrent VTE were 1.7% in each apixaban group compared to 8.8% in the placebo group (Table 1). Major bleeding events occurred in 0.2% in the 2.5 mg apixaban group, 0.1% in the 5 mg apixaban group, and in 0.5% of the placebo group. Clinically relevant bleeding (MB or CRNMB) events occurred in 3.2% of patients receiving apixaban 2.5 mg and 2.7% of those on placebo (cf. Table 2).

Table 1: Recurrent VTE event rates in Phase III VTE Secondary Prevention Trials

Study	Outcome	Comparator 1	Comparator 2	Hazard Ratio (95% CI)
RE-MEDY	Recurrent VTE or VTE-related death	Dabigatran: 1.2%	Warfarin: 0.87%	1.44 (0.78-2.64)
EINSTEIN-EXT	Recurrent VTE	Rivaroxaban: 1.3%	Placebo: 7.1%	0.18 (0.09-0.39)
AMPLIFY-EXT	Recurrent VTE or VTE-related death	Apixaban 2.5 mg BID: 1.7%	Placebo: 8.8%	Relative Risk: 0.19 (0.11-0.33)
AMPLIFY-EXT	Recurrent VTE or VTE-related death	Apixaban 2.5 mg BID: 1.7%	Apixaban 5 mg BID: 1.7%	Relative Risk: 0.97 (0.46-2.02)

Table 2: Clinically Relevant Bleeding (Major Bleeding [MB] and clinically relevant non-major bleeding [CRNMB]) event rates in Phase III VTE Secondary Prevention Trials

Study	Outcome	Comparator 1	Comparator 2	Hazard Ratio (95% CI)
RE-MEDY	MB or CRNMB	Dabigatran: 5.6%	Warfarin: 10.2%	0.54 (0.41-0.71)
EINSTEIN-EXT	MB or CRNMB	Rivaroxaban: 6.0%	Placebo: 1.2%	5.19 (2.3-11.7)
AMPLIFY-EXT	MB or CRNMB	Apixaban 2.5 mg BID: 3.2%	Placebo: 2.7%	Relative Risk: 1.20 (0.69-2.10)
AMPLIFY-EXT	MB or CRNMB	Apixaban 2.5 mg BID: 3.2%	Apixaban 5 mg BID: 4.3%	Relative Risk: 0.74 (0.46-1.22)

1.4 Clinical Experience with Study Agents

The standard oral anticoagulant that has long been used for extended treatment of VTE has been VKAs. Warfarin is the most common VKA available in North America and it is an effective anticoagulant that reduces the risk of recurrent VTE by >90% (Castellucci 2013). We have set the outcome of our comparative effectiveness study for superiority relative to warfarin. Despite its effectiveness, there are several limitations of warfarin use including the narrow therapeutic window, frequent INR monitoring to ensure patients remain in target range of 2-3, and many food and drugs interactions. The need to monitor INRs can be burdensome for patients and interfere with regular activities and functioning. DOACs have simplified anticoagulation treatment for many patients because they do not require laboratory monitoring for dosing adjustments. There are four DOACs available for treatment of VTE in the United States and Canada – dabigatran, edoxaban, rivaroxaban and apixaban. Edoxaban has not been studied for extended anticoagulation in VTE so we have excluded it from the trial. Dabigatran has been associated with higher rates of acute coronary syndromes in previous VTE trials and we excluded it from our proposed trial (Schulman 2012; Connolly 2009).

The DOACs rivaroxaban and apixaban were chosen as the intervention anticoagulants for the proposed trial. Rivaroxaban and apixaban are two Factor Xa inhibitors that are at least as effective and safe as warfarin for treatment of acute VTE (Einstein Investigators 2010; Buller 2012; Agnelli 2013a). Each DOAC has also been compared to placebo for extended anticoagulation in patients with VTE, demonstrating significantly lower rates of recurrent VTE and similar or lower rates of major bleeding events (Einstein Investigators 2010; Agnelli 2013b). The differences between the medications are in their dosing frequency as rivaroxaban is once daily and apixaban is twice daily. Both medications are currently approved by the FDA and Health Canada and are widely available from commercial pharmacies. Direct comparison of these anticoagulants to warfarin will enable us to determine whether they are as efficacious and as safe as warfarin for extended VTE treatment.

1.5 Rationale for COVET

Vitamin K antagonists were the only oral anticoagulants available for many years and DOACs have expanded the choices now available. Although the Einstein and Amplify trials have changed clinical practice management for patients with acute VTE, generalizability of their results for extended anticoagulation are limited for the following reasons: a) treatment duration was shorter than what would be expected for extended anticoagulation; b) the trials contained patients with both provoked and unprovoked VTE; c) the patients were highly selected from populations that do not reflect clinical practice; d) lack of head-to-head comparisons of DOACs. Only one trial comparing a DOAC (dabigatran) to VKA for extended anticoagulation has been done (Schulman 2012) and no comparative efficacy or safety data exists for rivaroxaban and apixaban relative to warfarin for extended anticoagulation; and e) previous clinical trials were sponsored by industry and there is no interest by the manufacturers to conduct head-to-head comparisons of anticoagulants. Our study will advance knowledge in this field as it is a pragmatic comparison trial that will potentially change practice and resolve the decisional uncertainty patients and clinicians face when choosing an anticoagulant for extended treatment.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Safety Objectives

In patients at high-risk for recurrent VTE, the COVET trial will

- Determine if apixaban is superior to warfarin, target INR 2-3, in the reduction of clinically relevant bleeding.
- Determine if rivaroxaban is superior to warfarin, target INR 2-3 in the reduction of clinically relevant bleeding.

2.2 Primary Efficacy Objectives

In patients at high-risk for recurrent VTE, the COVET trial will

- Determine if apixaban is non-inferior to warfarin, target INR 2-3, in the prevention of recurrent venous thromboembolism.
- Determine if rivaroxaban is non-inferior to warfarin, target INR 2-3, in the prevention of recurrent venous thromboembolism.

2.3 Secondary Objectives

In patients at high-risk for recurrent VTE, the COVET trial will

- Compare the rates of clinically relevant bleeding between apixaban and rivaroxaban.

2.4 Primary Safety Endpoint

Clinically relevant bleeding (composite of major bleeding (MB) and/or clinically relevant non major bleeding (CRNMB)) is the primary safety outcome which specifically addresses concerns relevant to all patients with VTE. Our criteria to define clinically relevant bleeding are consistent with those in the aforementioned VTE trials and published by the International Society on Thrombosis and Haemostasis (ISTH) (Kaatz 2015).

2.5 Primary Efficacy Endpoint

Recurrent VTE is the primary efficacy outcome, defined according to criteria described in the 2012 Chest Guidelines for Diagnosis of DVT (Bates 2012) and 2014 European Society of Cardiology Guidelines for Diagnosis of PE (Konstaninides 2014). This outcome is patient centered and important for all stakeholders given the clinical (symptoms of pain and discomfort), social, and economic burden associated with it.

2.6 Other Study Endpoints

- All-cause mortality
- Major bleeding
- Clinically relevant non-major bleeding

- Premature termination of study medication
- Vascular events (myocardial infarction, ischemic stroke)

These study endpoints will be defined in detail in the Clinical Event Classification (CEC) charter.

3. PATIENT SELECTION

3.1 Inclusion Criteria

To be eligible for this trial, patients must meet all of the following criteria:

- Have confirmed acute, symptomatic, first lower extremity proximal DVT and/or PE that is NOT associated with a transient risk factor. (See Table 2 for list of transient risk factors that would exclude the patient)
- Have completed an initial treatment course of oral anticoagulant therapy for 3-12 months and have a recommendation from their provider to continue anticoagulation indefinitely.
- Have the capacity to understand and sign an informed consent form.
- Be 18 years of age and older.
- Under the direct care of a healthcare provider for treatment of VTE for the length of time in the study.

3.2 Exclusion Criteria

If a patient meets any of the following criteria, he or she may not be enrolled in the study:

- Creatinine clearance (CrCl) < 30 mL/min as determined by Cockcroft-Gault formula documented within 3 months from date of consent
- Significant liver disease (Child-Pugh B or C)
- Concomitant use of medications that are strong P-glycoprotein or CYP3A4 inducers/inhibitors
- Another indication for chronic therapeutic-dose anticoagulation, such as atrial fibrillation (i.e., rivaroxaban, 10 mg daily, or apixaban, 2.5 mg twice daily, would not be appropriate therapy)
- A clinical indication for a specific anticoagulant regimen (e.g., warfarin with a target INR of 2-3 is recommended for patients with 'triple-positive' antiphospholipid syndrome).
- Life expectancy < 3 months
- Currently pregnant or breast feeding
- Unable / unwilling to pay for one (or more) of the treatment options
- Active Cancer defined as:
  - Diagnosed with cancer within the past 6 months; or
  - Recurrent, regionally advanced or metastatic disease;
  - Currently receiving treatment or have received any treatment for cancer during the 6 months prior to randomization; or
  - A hematologic malignancy not in complete remission
- Unwilling / unlikely to agree to follow up

These exclusion criteria are less stringent than the phase III RCTs (Einstein Investigators 2010; Agnelli 2013) and are pragmatic and reflective of real world patients who would receive DOACs (Thorpe 2009).

Table 2. Transient risk factors*

For a patient to be eligible to participate in COVET, the following transient risk factors should NOT have been present during the 3 months preceding the diagnosis of the qualifying VTE:

- Surgery with general anesthesia for greater than 30 min.
- Confined to bed in hospital (only 'bathroom privileges') for at least 3 days with an acute illness.
- Caesarean section.
- Estrogen therapy.
- Pregnancy or puerperium.

* Adapted from (Kearon 2016, J Thromb Haemost 2016)

4. STUDY DESIGN

The COVET study is a multi-center, randomized, open-label study of approximately 3000 patients who have confirmed acute symptomatic and unprovoked DVT/PE, have completed initial treatment of oral anticoagulation therapy for 3-12 months and are at high risk for recurrent VTE. Eligible patients who consent to participate in the study will be randomized to warfarin, apixaban, or rivaroxaban.

4.1 Overview of Study

This will be a multi-center trial conducted in the United States and Canada. Patients will be treated for a period of 12 months (see Figure). Treatment beyond this will be at the discretion of the treating physician.

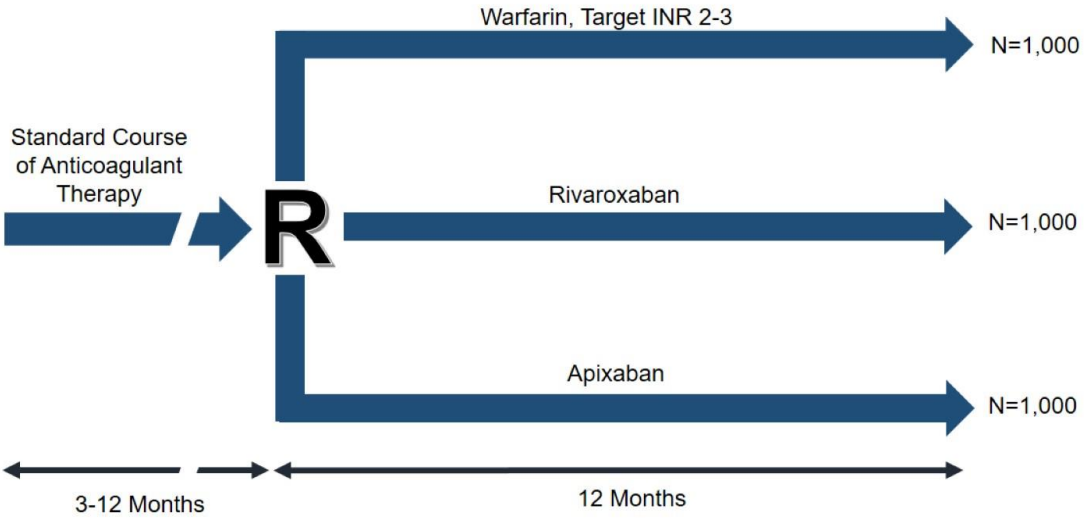

Figure. Study Design Schematic

4.2 Treatment Arms

After completion of an initial 3 to 12 months of anticoagulant therapy as standard of care, the patient will be randomized to receive one of the following therapies:

- Warfarin, target INR of 2-3
- Rivaroxaban, 10 mg daily
- Apixaban, 2.5 mg twice daily

Each study participant will be provided with detailed information describing how to switch from the anticoagulant that he/she was taking for their initial treatment, to the therapy that he/she will be taking for the study. The patient should start on the study-assigned anticoagulant within one week of randomization.

The possible transitions are described below:

a) Switching from warfarin to rivaroxaban

To switch from warfarin to rivaroxaban, stop the warfarin and determine the international normalized ration (INR). If the INR is ≤ 2.5, start rivaroxaban. If the INR is > 2.5, delay the start of rivaroxaban until the INR is ≤ 2.5. (Adapted from Rivaroxaban Product Monograph).

b) Switching from warfarin to apixaban

When switching patients from warfarin to apixaban, discontinue warfarin and start apixaban when the INR is below 2.0. (Adapted from the Apixaban Product Monograph).

c) Switching from rivaroxaban to warfarin

Rivaroxaban should be continued concurrently with warfarin until the INR is ≥ 2.0. For the first 2 days of the conversion period, the warfarin can be given in the usual starting doses without INR testing. Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of rivaroxaban, as appropriate. Rivaroxaban can be discontinued once the INR is >2.0. Once rivaroxaban is discontinued, INR testing may be done at least 24 hours after the last dose of rivaroxaban, and should then reliably reflect the anticoagulant effect of the warfarin. (Adapted from Rivaroxaban Product Monograph).

d) Switching from apixaban to warfarin

Apixaban should be continued concurrently with warfarin until the INR is ≥ 2.0. For the first 2 days of the conversion period, the warfarin can be given in the usual starting doses without INR testing. Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of apixaban, as appropriate. Apixaban can be discontinued once the INR is > 2.0. Once apixaban is discontinued, INR testing may be done at least 12 hours after the last dose of apixaban, and should then reliably reflect the anticoagulant effect of the warfarin. (Adapted from the Apixaban Product Monograph)

e) Switching from apixaban to rivaroxaban, or from rivaroxaban to apixaban

Switching from apixaban to rivaroxaban involves stopping the apixaban and beginning the rivaroxaban at the time of the next scheduled dose. Similarly, switching from rivaroxaban to apixaban involves stopping the rivaroxaban and beginning the apixaban at the next scheduled dose. (Recommendation by Principal Investigators consensus).

It is possible that some patients will be taking dabigatran or edoxaban for the initial treatment of their VTE. Transitions from these drugs would be performed as follows.

f) Switching from dabigatran to warfarin

Warfarin should be started while the patient is still taking dabigatran, adjusted according to the patient's calculated creatinine clearance (CrCl) as follows: CrCl ≥50 mL/min, start warfarin 3 days before discontinuing dabigatran; CrCl ≥30 to <50 mL/min, start warfarin 2 days before discontinuing dabigatran. Once dabigatran is discontinued, INR testing may be

done at least 48 hours after the last dose of dabigatran, and should then reliably reflect the anticoagulant effect of the warfarin. (Adapted from the Dabigatran Product Monograph)

g) Switching from edoxaban to warfarin

Warfarin should be started while the patient is still taking edoxaban. For the first 2 days of the conversion period, the warfarin can be given in the usual starting doses without INR testing. Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of edoxaban, as appropriate. Edoxaban can be discontinued once the INR is > 2.0. Once edoxaban is discontinued, INR testing may be done at least 24 hours after the last dose of edoxaban, and should then reliably reflect the anticoagulant effect of the warfarin. (Recommendation by Principal Investigators consensus).

h) Switching from dabigatran to rivaroxaban (or apixaban)

Switching from dabigatran to rivaroxaban (or apixaban) involves stopping the dabigatran and beginning the rivaroxaban (or apixaban) at the time of the next scheduled dose. (Recommendation by Principal Investigators consensus).

i) Switching from edoxaban to rivaroxaban (or apixaban)

Switching from edoxaban to rivaroxaban (or apixaban) involves stopping the edoxaban and beginning the rivaroxaban (or apixaban) at the time of the next scheduled dose. (Recommendation by Principal Investigators consensus).

Similarly, at the end of the study, each study participant will receive information from their primary physician on how to switch from the anticoagulant that they were on for the study to a post-study treatment plan.

4.3 Study Procedures

The follow-up schedule for research purposes will not require any in-person clinic visits (Table 3-Schedule of follow-up assessments). The only study related visit will be at the time of enrollment into the trial when the local research coordinator and investigator will review eligibility, obtain consent after answering questions, and proceed with randomization. All other trial related follow-up will be conducted remotely via structured telephone interviews at 1, 6, and 12 months. During regularly scheduled follow-up, patients will provide relevant information about events and if contact with a physician was made, medical records will be requested for review by the blinded CEC. The DCRI call center will contact the participants in the US. Canadian sites will contact the participants enrolled in Canada to complete the phone follow up and to collect medical records for CEC. Patients will also participate in two Patient Reported Outcomes measures, the Anti-Clot Treatment Scale (ACTS) and the EuroQol-5D-5L (EQ-5D-5L). These will be collected at Baseline, Month 1, Month 6 and Month 12. Regular clinic visits will be in keeping with local practices and at the discretion of the treating physician. Patients will be provided with a study participation journal to capture event information between scheduled study visits.

Our primary safety and main efficacy outcomes are important patient-reported outcomes measures (clinically relevant bleeding and recurrent VTE, respectively). Concerns for recurrent VTE or bleeding may require investigations that will be consistent with standard of care. Patients will be instructed on when to seek medical attention and local practices will determine

investigations and further management. Diagnosis of DVT will be confirmed by ultrasonography. If a patient experiences signs or symptoms suggestive of bleeding or recurrent VTE, and diagnostic tests are performed, all events will be treated according to the standard of care at the local institution by the primary physician.

4.4 Schedule of Follow-Up Assessments

Table 3: Schedule of Follow-up Assessments for Enrolled Participants

Time (Day)	Screening / Randomization	Month 1*	Month 6*	Month 12*
Visit	Visit 1	Visit 2	Visit 3	Visit 4
Visit Window	30 days	(+/- 1 week)**	(+/- 4 week)***	(+ 8weeks)
Type of Visit	In-person	Phone call	Phone call	Phone call
Patient consent	X			
Height and Weight	X			
Medical history	X			
Event assessment		X	X	X
Concomitant medication review/ Medication Compliance	X	X	X	X
ACTS	X	X	X	X
EQ-5D-5L	X	X	X	X

*Canadian participants will be contacted by the Canadian enrolling centers to complete phone assessments.

**If the participant is not reached within the +/- 1 week window, please attempt contact until Month 3.

*** If the participant is not reached within the +/- 4 week window, please attempt contact until Month 9.

4.5 Screening and Pre-randomization Procedures

Patients will be identified in outpatient clinical settings of hematologists and general internists in the U.S. and Canada. Recruitment of patients from such a setting is intentional so that we may enroll patients seen in daily practice to ensure generalizability of results at conclusion of the trial. The annual volume of patients at each participating center is variable with up to 10,000 patient visits, based on administrative data at each participating site. Daily clinic logs will be used to identify eligible patients, and patients who do not meet exclusion criteria will be approached to participate in the proposed trial. Many of these practice settings will also be affiliated with an anticoagulation clinic.

Patients who satisfy eligibility criteria will be approached to consider participation in the trial. A research coordinator or delegated site personnel will supply the patient with information and informed consent about the trial. The site personnel will also review with the patient anticipated out-of-pocket/copay costs for each of the study drugs. If the patient incurs a cost for any of the three treatment arms (either full cost of the medication, or a copay) that is not sufficiently off-set by the copay provided through the study, and the patient is unable and/or unwilling to cover that cost, then the patient should not be enrolled into the trial. As a pragmatic, real world study, the patient and his/her insurance company is responsible for the cost of the medical care (including labs such as INR, doctor visits, etc), as well as any medication costs not covered by the study.

After an appropriate amount of time to read the information and informed consent form has elapsed, the research coordinator and/or physician will answer any questions the patient and their family members may have. Patients agreeing to participate will then be enrolled, randomized and followed as outlined in the study protocol.

4.6 Randomization

We will use permuted block randomization with randomly selected block sizes through a central randomization system in a 1:1:1 ratio for the three treatments. The randomization scheme will be generated by an independent statistician. Blocks will be stratified by anticoagulant used (e.g. warfarin, apixaban, rivaroxaban, or other) to treat acute VTE event prior to randomization. The randomization process will be initiated by the local study coordinator/site investigator who will access the web-based system and enter the patient's unique identifier, center number, confirmation of eligibility and informed consent. Patient allocation will then be electronically delivered to the study coordinator and site investigator so that a prescription may be written for the corresponding anticoagulant. The patient will have the prescription dispensed at a local pharmacy as these are all commercially available medications. Co-pay assistance will be provided by the study through the use of the RxStudy Card™ (administered through RxSolutions). The cards will be available to all non-VA sites (unless prohibited by institutional policy). VA sites will not participate in the co-pay assistance program. Medication for the VA sites' patients will be provided by the affiliated VA pharmacies.

4.7 Post-randomization Procedures

The follow-up schedule for research purposes will not require any in-person clinic visits. The only study related visit will be at the time of enrollment into the trial when the local research coordinator and investigator will review eligibility, obtain consent after answering questions, and proceed with randomization. All other trial related follow-up will be conducted remotely via structured telephone interviews at 1, 6, and 12 months.

During regularly scheduled follow-up phone calls, patients will provide relevant information about any outcome event and if contact with a physician was made, medical records will be requested by the DCRI Call Center / Canadian site for review by the CEC. Regular clinic visits will be in keeping with local practices and at the discretion of the treating physician. Unscheduled study visits are not expected during this study. Patients will be provided with a study participation journal to capture event information between scheduled study contacts. These journals are provided to the patients as a tool to assist in reporting only and use is optional. The journals will not be used as a source document.

5. TREATMENT ARMS

Warfarin, rivaroxaban and apixaban will be prescribed and administered according to the approved dosages and indications.

5.1 Study Drug Administration

Patients will be randomized to receive either warfarin, rivaroxaban or apixaban. Warfarin will be given as needed to obtain a target INR of 2-3. Rivaroxaban will be prescribed at 10mg daily and apixaban will be prescribed at 2.5mg twice daily. Patients on once daily medications will have flexibility in determining the daily dosing timing. Patients will receive a prescription for the medication to which they are assigned.. The assigned medication will be dispensed at a local pharmacy.

5.2 Potential Benefits/Risks of Study Medications

All three of the anticoagulant agents included in this study have been shown to be efficacious in the secondary prevention of recurrent VTE (cf. Table 1). These three agents have not been directly compared, but indirect comparisons suggest that rivaroxaban and apixaban are not inferior to warfarin, target INR 2-3, in the prevention of recurrent VTE. In contrast, clinically relevant bleeding (combination of major bleeding and clinically relevant, non-major bleeding) appear to be lower for the direct oral anticoagulants compared to warfarin, target INR 2-3 (cf. Table 2). This study will address both of these issues with sufficient power to provide high-quality data to inform decisions.

The direct oral anticoagulants also offer several potential benefits to patients compared to warfarin, including no dietary restrictions affecting the efficacy of rivaroxaban and apixaban, and therapy with these two agents does not need to be monitored by laboratory testing. Conversely, concerns have been expressed by patients about the lack of a reversal agent for the factor Xa-specific agents in contrast to warfarin, where the anticoagulant effect can be reversed by administration of a prothrombin complex concentrate and/or vitamin K. Strategies have been developed for the treatment of bleeding complications in patients taking rivaroxaban and apixaban, however, and studies are ongoing with a specific reversal agent.

5.3 Procedure to Assess Medication Adherence

We will evaluate medication adherence by self-report from the participant. Medication adherence information will be collected at 1 month, 6 months, and 12 months.

5.4 Concomitant Medications

Concomitant medications will be assessed by site personnel during the screening/randomization visit (visit 1). Concomitant mediations will also be assessed during the follow-up period phone contact at 1 month, 6 months and 12 months.

5.5 Patient Reported Outcomes/Quality of Life Assessments

5.5.1 Anti-coagulant Treatment Scale

The patient satisfaction question that will be addressed by COVET is whether patients are more satisfied with chronic anticoagulant therapy with apixaban or rivaroxaban compared to warfarin with a target INR of 2-3. To address this question, we will use the Anti-Clot Treatment Scale (ACTS), a 15-item patient-reported instrument that includes a 12-item ACTS Burdens scale and a 3-item ACTS Benefits scale. Patients are asked to rate their experiences of anticoagulant treatment during the preceding 4 weeks on a 5-point scale of intensity (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, 5 = extremely). The ACTS Burdens total score ranges from 12 to 60, and the ACTS Benefits total score ranges from 3 to 15. In this study, the ACTS scale will be administered at baseline, 1 month, 6 months, and 12 months. In the US, the baseline ACTS scale will be performed by the site enrolling the patient, and the scales for the 1, 6, and 12 month calls will be administered by the Call Center. In Canada, all of the scales will be performed at the site enrolling the patient.

5.5.2 EQ-5D-5L

The economic research question is whether using apixaban and rivaroxaban for treatment of acute VTE is cost-effective compared to warfarin. In this study, the EQ-5D-5L will be administered at baseline, 1 month, 6 months, and 12 months. In the US, the baseline EQ-5D-5L scale will be performed by the site enrolling the patient, and the scales for the 1, 6, and 12 month calls will be administered by the Call Center. In Canada, all of the scales will be performed at the site enrolling the patient.

5.6 Prohibited Medications

The concomitant use of medications that are strong P-glycoprotein or CYP3A4 inducers/inhibitors is prohibited due to interactions with rivaroxaban and apixaban. Examples include: all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically.

Use of single or dual antiplatelet agents is not prohibited.

5.7 Peri-Procedural anticoagulation management

Please refer to the following resources for recommendations regarding anticoagulant interruption.

1) Thrombosis Canada: (http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm)

2) Spyropoulos AC, Douketis, JD. "How I treat anticoagulated patients undergoing an elective procedure or surgery" Blood, 2012; 120: 2954-62.

3) Douketis JD, Spyropoulos AC, et al. "Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines" Chest, 2012; 141 (2 Suppl): e326S-50S.

6. SAFETY ASSESSMENTS

6.1 Safety Assessments and Reporting

All study medications will be prescribed and administered per the approved package insert. For this trial the defined safety outcome events of interest will be recorded in the electronic case report form (eCRF) by site personnel and/or the follow-up call center personnel. If site personnel become aware of a treatment-related event that is considered serious and unexpected, the site investigator should report the event to the local IRB/ethics committee per local policy.

6.2 Adverse Events

The COVET study is designed to be a pragmatic trial comparing three therapeutic agents approved by the regulatory agencies in the United States (Food and Drug Administration) and Canada (Health Canada) for the extended treatment of patients with an unprovoked DVT or PE to prevent recurrent thromboembolism. We will be collecting adjudicated outcome events, including bleeding, that have been shown to account for the majority of SAE's based on a large number of patients treated in several clinical studies. These outcome events, listed above in Section 2, include the following:

- Clinically relevant bleeding, which is the composite of major bleeding and/or clinically-relevant, non-major bleeding, as defined by ISTH criteria (Kaatz, 2015)
- Recurrent VTE, as defined above (Section 2.5), representing failure in efficacy
- All-cause mortality
- Vascular events, including myocardial infarction and ischemic stroke

All study endpoints will be identified during scheduled contact with the study participants at 1 month, 6 months, and 12 months (see Table 3) and reported to the P.I., co-P.I.'s, and study leadership at DCRI within 24 hours. All events will then be independently adjudicated by the Clinical Event Classification committee (section 11.9).

Pregnancy is also collected as part of the COVET study (section 6.3) and will be reported within 24 hours as described for the outcome events documented above.

Study drug discontinuation is also collected as part of the COVET study, including the reason for discontinuation of the study drug. Laboratory tests are not being collected in the COVET study.

6.3 Pregnancy

If a participant becomes pregnant during the course of the study and they elect to carry the pregnancy to term, the following actions should be taken:

1. The patient should notify the site investigator immediately
2. The study anticoagulant will be discontinued
3. The local investigator will decide what (if any) ongoing anticoagulation therapy will be prescribed (off study)
4. The patient may continue with the follow-up telephone calls only.

A separate document for women of childbearing age regarding instructions if she becomes pregnant will be provided at enrollment into the trial. These instructions will include discussing discontinuation of the study anticoagulant with their primary care physician (PCP), notifying their study doctor (if different from their PCP) of the pregnancy and the ability to continue participation in the study once the study medication has been discontinued.

6.4 Criteria for Withdrawal of Patients from Study

Participants have the right to withdraw from the study at any time and for any reason without prejudice to future medical care. In the case of participant withdrawal, the investigator will discuss with the patient the most appropriate way to terminate study participation to ensure the patient's health. All efforts will be made to complete and report the observations as thoroughly as possible up to the date of study termination. All applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Randomized patients who withdraw from the study will not be replaced.

7. STATISTICAL CONSIDERATIONS

7.1 General Design Issues

COVET is a 3-arm prospective, multi-center, open-label, active comparator, randomized study designed to compare the efficacy and safety of apixaban and rivaroxaban compared with standard warfarin therapy. All potential study endpoints will be reviewed by a central adjudication committee that is blinded to treatment assignment. For participants who withdraw consent for follow-up, all data obtained prior to the time of formal withdrawal will be used in data analyses. The duration of follow up from randomization is expected to be twelve months, and all participants will be expected to remain in study until the 12-month follow-up telephone call regardless of whether they are taking their assigned study medication. Reporting of this prospective, randomized, open-label, blinded endpoint design will follow the CONSORT recommendations (Hansson 1992; Paggio 2012).

The primary efficacy endpoint is rate of recurrent VTEs and the primary safety endpoint is clinically relevant bleeding. Secondary endpoints include components of the primary endpoints, all-cause mortality, and other events of interest. The primary efficacy and safety endpoints will be confirmed by a CEC. Participants will be randomized in a 1:1:1 ratio to warfarin, apixaban, or rivaroxaban. Randomization will be stratified by the anticoagulant used during the screening period. For purposes of randomization, the screening anticoagulants will be classified as either warfarin, apixaban, rivaroxaban, or other. The relative open inclusion criteria, limited exclusions, and simple follow-up structure of COVET are an attempt to be pragmatic (Thorpe 2009).

SAS software version 9.4 or higher will be used for all statistical analyses. P-values less than 0.05 will be considered statistically significant unless otherwise specified. Complete details of all planned analyses will be contained in a separate Statistical Analysis Plan (SAP). The SAP will include the planned tables, listings, and figures. In particular, special attention will be given the participants who do not have complete data.

7.2 Sample Size Justification

The planning and sample size calculations for the COVET study were designed to compare warfarin vs. apixaban and warfarin vs. rivaroxaban. A direct exploratory and descriptive comparison of the two DOACs will be conducted but the study was not powered to detect statistically significant differences between those treatment groups.

For the primary safety endpoint, there will be two comparisons, apixaban versus warfarin and rivaroxaban versus warfarin, each of which will be tested at the two-sided 0.05 level of significance to detect a 50% reduction (HR=0.50) in clinically relevant bleeding compared to warfarin. For the primary efficacy endpoint, there will be two comparisons, apixaban versus warfarin and rivaroxaban versus warfarin to determine if the DOACs are non-inferior to warfarin in the prevention of recurrent venous thromboembolism. The non-inferiority assessments will be based on comparing the one-sided 95% upper confidence interval with a 2% absolute risk increase for recurrent VTE.

The type I error rates for the non-inferiority and superiority analyses have been set at 0.05 one-sided and 0.05 two-sided, respectively. These are considered standard values for two

arm studies. We have elected to not alter them for this three-arm design because the clinical questions of interest are the two comparisons of the DOACs versus warfarin.

For the primary efficacy analysis, using an outcome of recurrent VTE, we expect 12-month rate of 0.87% for the warfarin arm compared with 1.5% for the DOACs (Einstein Investigators 2010; Agnelli 2013). Sample sizes of 950 per arm are sufficient to provide 80% power to have the upper 95% one-sided confidence interval less than 2%. The proposed sample size of 1000 participants per arm allows for 5% missing data due to loss-to-follow-up, deaths not related to VTE, and lack of starting the assigned study drug. These calculations were obtained using a simulation method with nQuery Advisor 7.0 software.

For the primary safety analysis, the RE-MEDY study reported clinically relevant bleeding rates of 10.2% for the warfarin treated patients (Schulman 2013). Using a 12-month rate of 6.8%, a per group sample size of 950 participants (or 1000 / group with an allowance for 5% missing data) will provide greater than 90% power to detect a 50% event rate reduction for the DOAC arm. Similarly, assuming a lower 12-month event rate of 6.0% for the warfarin arm, the sample size of 950 participants per group will provide 88% power to detect a 50% event rate reduction for the DOAC arm. These calculations assume a two-sided 0.05 type I error rate and are based on a Cox model.

7.3 Definition of Analysis Populations

All-randomized (Intention To Treat-ITT) population
This population includes all randomized participants regardless of the actual treatment received. This population will be used for the primary analysis of the primary safety and efficacy endpoints.

Per protocol population
This population excludes participants who have not started the assigned therapy by the time of the 1 month telephone interview. For time-to-event analyses, participants who stop taking the assigned treatment will be censored after permanently stopping the assigned treatment.

7.4 Interim Analyses and Stopping Rules

There will be no formal interim analyses for the primary efficacy or safety endpoints for futility. The Data and Safety Monitoring Board (DSMB) will meet regularly to review patient safety and overall study conduct. The independent DSMB will review the summaries of patient safety and self-reported adherence at regular intervals.

Pooled event rates for the primary safety and primary efficacy and per-protocol anticoagulant adherence will be reviewed by the Steering Committee after 500, 1000, and 1500 participants have completed the 12-month telephone contact. The overall sample size will be assessed based on a comparison of the observed rates with the rates used for the sample size estimates.

7.5 Data Analyses

Baseline characteristics will be presented using mean (standard deviation) and median (25^{th}, 75^{th} percentiles) for continuous variables and as frequencies (percentages) for categorical variables. No formal comparisons will be computed for baseline variables.

The primary analyses for safety primary endpoint will be based on an un-stratified Cox model adjusting for the two treatment indicators and three stratification indicators. The ascertainment time will be based on the time of the first event or censoring time. Stratification will be based on the anticoagulant used during the screening period. The all-randomized (ITT) analysis dataset will be used for the primary analyses. The treatment effect for each DOAC compared to warfarin will be computed using the estimated hazard ratio and associated 95% confidence intervals. Secondary analyses will be based on a Kaplan-Meier estimates on the all-randomized (ITT) and per-protocol populations.

For the efficacy primary endpoint, the primary analysis will be based on a Kaplan-Meier analysis using the all-randomized (ITT) analysis dataset. The 12-month event rates differences between the DOACs versus warfarin will be based on the difference in the Kaplan-Meier estimates and the one-sided upper 95% confidence interval will be based on a bootstrap estimator. Secondary analyses of the recurrent VTE endpoint will be based on the Cox regression model. Exploratory analyses will directly compare the two DOACs for both safety and efficacy endpoints. Additionally, an exploratory analysis will pool the two DOAC arms and compare those estimates with the warfarin treatment group.

For secondary endpoints, the estimated differences between the DOACs and warfarin treated groups will be based on linear models, logistic regression, and Cox models depending on the endpoint. Efforts will be made to limit the amount of missing data for the key endpoints and adherence measures. When necessary, multiple imputation will be used to account for missing covariate information.

The SAP will contain details on sensitivity analysis that will be done to support the previously described analyses. There are two particular issues that might create biased estimates – missing data and lack of adherence to the assigned treatment. For the missing data problem, we will impute data with higher, same, and lower event rates for the DOAC arms to estimate the impact of missingness on the study results. In addition to the analyses with the all randomized dataset, we will conduct analyses with the per-protocol dataset to determine the impact of participants not taking the assigned study drug. For the per-protocol analyses there is no guarantee that the comparisons are valid based on randomization. To account for this potential bias, inverse probability weighted (IPW) estimators will be used to re-weight the per-protocol population. The IPW weights will be obtained using logistic regression models predicting adherence at 1 month. The SAP will also address analysis of the Patient Reported Outcomes tools, the ACTS and the EQ-5D-5L.

The study investigators have identified several pre-specified subgroups of interest. Those subgroups include: initial anticoagulant, race, sex, renal impairment, obesity, and antiplatelet use (Buckner 2012; Liao 2014; White 2009). Given the expected low number of events for both primary endpoints, the subgroups will need to be interpreted

cautiously. For each subgroup we will compute an interaction p-value and then estimate hazard ratios for each subgroup.

8. FOLLOW-UP DATA COLLECTION AND CLINICAL EVENT CLASSIFICATION

Participants will be provided with instructions to maintain a diary during the course of the study to facilitate reporting of events at the time of the follow-up calls. For participants in the US, the DCRI Call Center will attempt phone calls at 1 month, 6 months and 12 months following randomization. For participants enrolled at Canadian sites, the enrolling site will contact the participant at the same time intervals. Information collected during these phone calls will be documented in the eCRF. If a participant reports that they are experiencing an event during a scheduled call, the Call Center agent will advise the participant to contact their health care provider or call 911 if it is an emergency. The event details would be captured at the next scheduled call. Medical records associated with all potential outcome events will be requested/obtained and sent to the blinded CEC for review.

COVET is comparing treatment strategies that are already in standard clinical use, and it is not anticipated that outcomes beyond those that can be seen in any patient taking anticoagulant therapy will be encountered. For each outcome event, supporting documentation to include all radiographic imaging data, relevant laboratory data, and treatment records will be collected by the centralized call center for review and validation. All outcomes will be independently adjudicated by physician reviewers with expertise in thrombosis who will be blinded to the specific treatment arm to which the patient had been randomized. Outcome classification will follow an established protocol similar to prior studies conducted through the DCRI. Details of the clinical event adjudication process will be included in the CEC Charter.

9. DATA MANAGEMENT AND QUALITY ASSURANCE

9.1 Data Management

All required data for this study will be entered into the electronic case report form (eCRF). This study will use Web-based e-CRFs developed through a validated, electronic reporting-electronic-signatures–compliant platform (21 Code of Federal Regulations Part 11). For security reasons, and in compliance with regulatory guidelines, it is imperative that only the persons who own the user IDs and passwords access the system using their own unique access codes. Access codes are nontransferable. Site personnel who have not undergone training may not use the system and will not be issued user ID and password until appropriate training is completed.

At the conclusion of the study, each enrolling site will be provided with a compact disc containing PDF files of both the individual patient's data and the audit trail (changes made to the database). This will be maintained at the site according to the requirements for records retention.

Computerized data will be accessible only by password, and a centralized monitoring system will record and report all access to data. The DCRI computer network is protected by a firewall. To ensure participant anonymity, eCRFs will be identified by study number only. No participant identifiers will be used in the presentation of data. Except when required by law, participants will not be identified by name, personal identification number (e.g. social security number, social insurance number), address, telephone number, or any other direct personal identifier in study records. This information will be retained by each individual center and will not be disclosed to the DCRI except as needed for centralized follow-up of the participants. Participants will be informed that their records may be reviewed in order to meet federal, state or regional/local regulations. Reviewers may include the study monitors, IRBs or Ethics Committees, and other government regulators as dictated by local law, or their delegates.

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the DCC must be notified in writing and be given the opportunity to further store such records.

9.2 Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include:

- the selection of qualified investigators and appropriate study centers
- review of protocol procedures with the investigator and associated personnel before the study
- periodic monitoring visits to clinical sites

- electronic CRF completion guidelines will be provided and reviewed with study personnel before the start of the study.

- The DCRI clinical research associate will review eCRFs for accuracy and completeness during site monitoring; any discrepancies will be resolved with the investigator or designee, as appropriate.

At regular intervals, all data will be transferred from the study database to SAS for statistical summarization, data description, and data analysis. Further cross-checking of the data will be performed in SAS, and discrepant observations flagged and appropriately resolved through a data query system.

10. STUDY RESPONSIBILITIES

10.1 Investigator Responsibility/Performance

The site principal investigator (PI) agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol; accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The site PI will provide current copies of the study protocol to all sub-investigators or other site personnel responsible for study conduct. Additionally, the site PI will provide DCRI with copies of all institutional review board (IRB) or Ethics Committee actions regarding the study.

10.2 Training

The initial training of appropriate clinical site personnel will be the responsibility of the DCRI. The PI is responsible for ensuring that staff conduct the study according to the protocol. To ensure proper administration of study agents, uniform data collection, and protocol compliance, the DCRI will present a formal training session to study site personnel, to include instructions for study procedures, the investigational plan, instructions on data collection, methods for soliciting data from alternative sources, and regulatory requirements.

10.3 Monitoring the Investigational Sites

As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of GCP and applicable regulations, a study monitor from the DCRI will visit the study sites as appropriate and will maintain frequent telephone and written communication.

Remote monitoring will be used for this study. Site managers will schedule monitoring calls to review enrollment, EDC completion, informed consent and overall study management. During monitoring visits, the monitor will perform a review of inclusion/exclusion criteria, informed consent, HIPAA authorization, as well as safety and efficacy endpoints. Sites may be required to provide at a minimum the informed consent and eligibility requirements for patients to the sponsor or designee via a secure system.

Trends will be monitored and, if warranted, the frequency of onsite monitoring visits may be adjusted at sites. Details will be described in the clinical monitoring plan

On-site monitoring visits may be performed at active investigational sites as needed to assure that the investigator obligations are being fulfilled and all applicable regulations and guidelines are being followed. These visits will be initiated based on the findings of monitoring calls and/or data review. The goal of these on-site visits are to assure the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB or Ethics Committee has been notified of approved protocol changes as required, complete records are being maintained, appropriate reports have been made to the

sponsor or designee and the IRB or Ethics Committee, and the investigator is carrying out all agreed-upon activities.

10.4 Study Documentation

Study documentation includes all electronic case report forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and regulatory documents (e.g., protocol and amendments, IRB or EC correspondence and approval, approved and signed patient consent forms, Patient contact forms and medical release forms).

The site PI will prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations. For each patient participating in the study at the site, the investigator will promptly complete all eCRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the sponsor.

The site PI acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to the sponsor or designee by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the sponsor or responsible government agencies as required by law.

The site PI agrees to promptly take any reasonable steps that are requested by the sponsor or designee as a result of an audit to cure deficiencies in the study documentation and eCRFs.

10.5 Source Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports, electrocardiogram (ECG) tracings, x-rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs, patient progress notes, hospital charts, pharmacy records, and any other similar reports or records of any procedure performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

10.6 Protocol Deviations

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the study according to the investigational plan. Site investigators must also follow the policy of the reviewing IRB for reporting such deviations to their reviewing IRB per local policy.

The IRB or Ethics Committee will be informed of all protocol changes by the sponsor or the investigator in accordance with applicable regulations and the IRB or Ethics

Committee's established procedures. No deviations from the protocol of any type will be made without complying with the IRB or Ethics Committee's established procedures. Investigators will maintain documentation of the dates and reasons for each deviation from the protocol.

10.7 Data Transmittal and Record Retention

Required data will be entered in the eCRF at the time of or as soon as possible after the patient call/visit or the availability of test results. The site PI will maintain final eCRFs, worksheets, and all other study-specific documentation (e.g., study file notebooks or source documentation) until notified by the sponsor that records may be destroyed. To avoid error, the investigator will contact the sponsor or designee before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, the sponsor or designee will be contacted if the PI plans to leave the institution so that arrangements can be made for the transfer of records. The site PI takes responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor or designee as well as by federal, state, and local regulatory agencies.

10.8 Study Closeout

Upon completion of the study (defined as all patients have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved), the sponsor or designee will notify the site of closeout, and a study closeout visit will be performed via telephone. All unused study materials can be destroyed by the site when the study is completed. The sponsor or designee will ensure that the site PI's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

10.9 Audit/Inspections

Regulatory authorities from the U.S. or abroad may inspect the site during or after the study at a reasonable time and in a reasonable manner. The site PI should contact the sponsor immediately if contacted regarding an inspection. Site personnel are expected to cooperate with personnel from regulatory agencies (e.g., FDA and Health Canada).

10.10 Publication Policies

Members of the Steering Committee will be primarily responsible for creation, review, and submission of publications and presentations relating to the major aspects of the study and approved ancillary analyses within a timely fashion after completion of the study. Details will be contained in the Publication Plan.

11. ETHICAL CONSIDERATIONS

11.1 Informed Consent

The PI has both ethical and legal responsibility to ensure that each patient being considered for inclusion in this study is given a full explanation of the study. Written informed consent will be obtained from all patients (or, at the discretion of the local IRB, the patient's guardian or legally authorized representative [LAR]) before any study-related procedures are performed or given.

Written informed consent will be documented on an informed consent form (ICF) approved by the local IRB/EC responsible for approval of this protocol. The ICF will conform to the applicable requirements of 45 CFR 46, ICH E6 and institutional requirements for informed consent. The site investigator agrees to obtain approval from DCRI of any ICF intended for use in the study before submission of the ICF for IRB approval.

11.2 Confidentiality of Patients

Patient confidentiality will be maintained throughout the clinical study in a way that ensures that study data can always be tracked back to the source data. Patient information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated by the U.S. Health Insurance Portability and Accountability Act (HIPAA). All records will be kept confidential, and the patient's name and contact information will not be released for US participants to persons other than the DCRI Call Center. Patient records will not be released to anyone other than DCRI or its designees and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the patient's privacy is guaranteed. The DCRI call center will contact the participants in the US. Canadian sites will contact the participants enrolled in Canada to complete the phone follow up and to collect medical records for CEC. Any records sent from the Canadian sites to DCRI for endpoint review will have PHI redacted prior to providing to DCRI.

11.3 Authorization for Use and Disclosure of Protected Health Information

An authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule will be obtained from every trial patient before enrollment. The investigator is responsible for obtaining patients' (or their LARs') authorizations and signatures and for explaining the elements of the HIPAA authorization form, if necessary.

The site PI will promptly inform DCRI of any restrictions on the use or disclosure of any patient's PHI. The site investigator will also promptly inform the sponsor of written revocation of any patient's HIPAA authorization.

11.4 Human Subject Protections

11.4.1 Research Subject Selection and Justification of Exclusions

There will be no exclusion from participation in the study on the basis of ethnicity or race. Subjects younger than 18 years of age will be excluded from the study, as the target population is adults.

11.4.2 Risks/Discomforts of Study Participation

This study will evaluate the safety and efficacy of warfarin, apixaban and rivaroxaban in patients at high risk for recurrent VTE. These medications are standard of care for treatment of VTE.

11.5 Institutional Review Board/Ethics Committee Review

The appropriate IRB or Ethics Committee must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The investigator will provide DCRI with documentation that the IRB or Ethics Committee has approved the study ***before*** the study may begin.

In addition, the investigator must provide the following documentation to DCRI:

1. IRB or Ethics Committee annual re-approval of the protocol,

2. IRB or Ethics Committee approval of revisions to the informed consent documents or any amendments to the protocol. The investigator will provide DCRI or designee with documentation of all approvals.

11.6 Steering Committee

The Steering Committee will be the primary decision making body of the study and is responsible for its successful completion. The Steering Committee will be comprised of the study principal investigators, the project leader, and selected other investigators with expertise in venous thromboembolism, anticoagulation, biostatistics, and clinical trials.

11.7 Study Advisory Committee (SAC)

Members of the SAC with include the PI, co-PIs, two patient partners, a patient partner physician leader, researchers, and several professional stakeholders (i.e. payers, industry, purchasers) who will act as consultants to the SAC. The SAC will be responsible for engagement activities to identify patient-oriented outcomes and provide recommendations based on each stakeholder member's interests. They will be instrumental in providing updates on patient recruitment and milestones. Opinions and feedback from the professional stakeholders will reinforce that "real-world" concerns are addressed during the trial and that the results can be utilized by all stakeholder end-users. Members of the SAC will be instrumental in dissemination of the trial results to ensure they can be adopted by their respective end-users. The SAC will report to the Steering Committee any recommendations made from the SAC engagement activities and stakeholders. For example, issues arising during the trial, such as slow recruitment rates, would be reviewed by the SAC for discussion and brainstorming with stakeholders. These recommendations would be brought to the Steering Committee for further consideration and approval before execution of a plan.

11.8 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will be appointed for the COVET trial, which will include individuals with pertinent expertise in anticoagulation, clinical trials, and biostatistics. The DSMB will advise the Steering Committee regarding participant reported safety events of interest for current participants.

The composition of the DSMB will be specified in the overall DSMB Charter for the study. It is anticipated that the board will include a (1) chair with both clinical and research expertise in anticoagulant therapy, (2) a senior statistician with prior DSMB experience; and (3) a member of the community. A DSMB Charter for the studies will be developed detailing specific data tables to be provided and procedures to be followed. The DSMB Charter will also describe the overall mission, responsibilities, and meeting schedule of the board. The following outlines the procedures for the DSMB. The DCRI statistical team will be responsible for assuring that the DSMB Charter is developed and approved. The Charter will be distributed to the members of the Study Advisory Committee for their review.

The goal of the DSMB will be to monitor patient safety and to review performance of the protocol. At the conclusion of each DSMB meeting, the DSMB Chair will make a recommendation to the Steering Committee and the Study Advisory Committee about the continuation of the study. Currently, we are planning that the DSMB will meet every six months via teleconference. If safety issues arise, additional conference calls can be requested by the DSMB chairman.

Confidential Interim Data Reports will be prepared regularly by the protocol statistician as specified in the Charter. The report will include recruitment and retention rates, outcomes, and other information as requested by the DSMB Chair. We anticipate that in accordance with customary PCORI practices, there will be both an open and closed session for the DSMB meeting.

11.9 Independent Clinical Events Classification (CEC)

The CEC committee will provide independent central adjudication of bleeds, recurrent VTE, and deaths. The guidelines for the adjudication process will be reported in a separate document, the CEC Charter. The members of this Committee will not participate in the enrollment or treatment of patients in this trial, nor will they participate in the DSMB.

11.10 Role of PCORI as a Funding Source

The Patient-Centered Outcomes Research Institute (PCORI) is an independent, nonprofit organization authorized by Congress in 2010. Its mission is to fund research that will provide patients, their caregivers, and clinicians with the evidence-based information needed to make better-informed healthcare decisions. PCORI is committed to continually seeking input from a broad range of stakeholders to guide its work.

12. REFERENCES

Agnelli G, Prandoni P, Santamaria MG et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med 2001;345(3):165-169.

Agnelli G [2013a], Buller HR, Cohen A et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368(8):699-708.

Agnelli G [2013b], Buller HR, Cohen A et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med 2013;369(9):799-808.

Apixaban: http://packageinserts.bms.com/pi/pi_eliquis.pdf (May 15, 2017)

Bates SM, Jaeschke R, Stevens SM et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e351S-e418S.

Buckner TW, Key NS. Venous thrombosis in blacks. Circulation 2012;125(6):837-839.

Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287-1297.

Canadian Agency For Drugs And Technologies In Health. *Guidelines for the economic evaluation of health technologies*. 4th ed. Ottawa: CADTH, 2017.

Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 2010;152(9):578-589.

Castellucci LA, Cameron C, Le Gal G et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ 2013;347:f5133.

Chan AW, Tetzlaff JM, Altman DG et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207.

Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009;361(12):1139-1151.

Dabigatran:
http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf (May 15, 2017)

Einstein Investigators, Bauersachs R, Berkowitz SD et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010;363(26):2499-2510.

Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;1(2):113-119.

Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Thrombolysis* 2006;21:23-29. PMID: 16475038

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., Badia, X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research* 2011 Dec; 20(10):1727–1736.

Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015 Nov;13(11):2119-26.

Kearon C, Gent M, Hirsh J et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999;340(12):901-907.

Kearon C, Akl EA, Comerota AJ et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e419S-e494S.

Kearon C, Akl EA, Ornelas J et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149(2):315-352.

Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J and Kyrle PA, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016; 14: 1480–3.

Konstantinides SV, Torbicki A, Agnelli G et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)Endorsed by the European Respiratory Society (ERS). Eur Heart J 2014;35(43):3033-3073.

Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med* 2004;350(25):2558-2616. PMID: 15201412

Liao S, Woulfe T, Hyder S, Merriman E, Simpson D, Chunilal S. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. J Thromb Haemost 2014;12(2):214-219.

Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012;308(24):2594-2604.

Prandoni P, Lensing AWA, Cogo A et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125(1):1-7.

Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Lancet 1992;340(8824):873-876.

Rivaroxaban: https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf (May 15, 2017)

Rodger MA, Kahn SR, Wells PS et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ 2008;179(5):417-426.

Schulman S, Rhedin AS, Lindmarker P et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. N
Engl J Med 1995;332:1661-1665.

Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692-694.

Schulman S, Kearon C, Kakkar AK et al. Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. N Engl J Med 2013;368(8):709-718.

Spyropoulos AC, Douketis, JD. "How I treat anticoagulated patients undergoing an elective procedure or surgery" Blood, 2012; 120: 2954-62.

Thorpe KE, Zwarenstein M, Oxman AD et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. CMAJ 2009;180(10):E47-E57.

Thrombosis Canada:
(http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

Vilchez JA, Gallego P, Lip GY. Safety of new oral anticoagulant drugs: a perspective. Ther Adv Drug Saf 2014;5(1):8-20.

White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107:I4-I8. PMID: 12814979

White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res 2009;123 Suppl 4:S11-S17.