PROTOCOL NUMBER: 2018P002307
DATE: 7/5/2023
VERSION NUMBER: 8
VERSION DATE: 7/5/2023

CLINICAL PROTOCOL

NEW-AF: Trial of **New** Oral Anticoagulants vs. **W**arfarin for post Cardiac Surgery **A**trial **F**ibrillation

Massachusetts General Hospital Division of Cardiac Surgery
55 Fruit Street
Boston, MA 02114
Phone: 617-643-9745
Phone 2: 617-726-2000 (Page 25948)

July 5, 2023

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I) TABLE OF CHANGES

VERSION / DATE	SUBSECTION	PAGE	CHANGE/RATIONALE
1 / Oct 1, 2018	NA	NA	NA
2 / Nov 19, 2018	Trial Summary/Abstract	5	Streamlined description of study design and hypothesize to make it clear that length of stay is the only primary outcome
2/ Nov 19, 2018	Trial Summary/Abstract	6	Moved description of major bleeding from "Primary Safety Outcome" to "Secondary Outcome." This clearly establishes length of stay as the only primary outcome
2/ Nov 19, 2018	Endpoints	12	Made major bleeding a secondary study endpoint instead of putting it in its own category as a "Primary safety endpoint." Done in response to IRB concerns about lack of clarity in description of the primary study outcome
2/ Nov 19, 2018	Subject Enrollment	16	Plan for consent changed so that consent will now by obtained only by licensed physician investigators. Study nurses and coordinators will not be able to independently obtain consent. This change was made in response to IRB request that consent be obtained by licensed providers
2/ Nov 19, 2018	Subject Enrollment	17	Study design changed and updated to exclude patients without mental capacity to provide consent. Change made in response to IRB request to exclude patients without capacity to provide consent for themselves
2/ Nov 19, 2018	Study Procedures and Design	19	More detail provided about plan for anticoagulation therapy and/or transition at study exit. Change made in response to IRB request to clarify the procedures at study exit
2/ Nov 19, 2018	Biostatistical Analysis Plan	28	More detail provided about plan for anticoagulation therapy and/or transition at study exit. Change made in response to IRB request to clarify the procedures at study exit
2/ Nov 19, 2018	Biostatistical Analysis Plan	30	Citation provided for estimations used to guide sample size calculations. Citation requested by IRB
3/ Feb 25, 2019	Trial Summary / Abstract	7	Added 'intra-cranial bleeding' to definition of major bleeding. Clarification requested by IRB
3/ Feb 25, 2019	Trial Summary / Abstract	7	Sample size calculations updated to reflect increased anticipated standard deviations based on recommendations from Biostatisticians
3/ Feb 25, 2019	Subject Selection	11	Moderate to severe mitral stenosis added to exclusion criteria based on IRB request to clarify the exclusion of patients with "valvular atrial fibrillation"

3/ Feb 25, 2019	Endpoints	13	Added 'intra-cranial bleeding' to definition of major bleeding. Clarification requested by IRB
3/ Feb 25, 2019	Study Procedures and Designs	19	Options for PCP, cardiologist or AMS follow up of INR described in more detail. Clarification of AMS role requested by IRB
3/ Feb 25, 2019	Biostatistical Analysis Plan	29	Options for PCP, cardiologist or AMS follow up of INR described in more detail. Clarification of AMS role requested by IRB
3/ Feb 25, 2019	Biostatistical Analysis Plan	30	Sample size calculations updated to reflect increased anticipated standard deviations based on recommendations from Biostatisticians
4/ Feb 28, 2019	Trial Summary/Abstract	6	Exclusion criterion changed from GFR < 15 ml / min to GFR < 30 ml / min based on concerns raised by IRB about safety in patients with very low GFR
4/ Feb 28, 2019	Subject Selection	11	Exclusion criterion changed from GFR < 15 ml / min to GFR < 30 ml / min based on concerns raised by IRB about safety in patients with very low GFR
4/ Feb 28, 2019	Study Procedures and Design	23	Lower limit of range for renal dosing of Rivaroxaban changed from "15ml/min" to "30ml/min" to reflect updated exclusion of patients with GFR < 30ml/min
5/ June 25, 2020	Trial Summary/Abstract	6	Added "Positive for SARS-COV-2 at time of surgery" to exclusion criteria.
5/ June 25, 2020	Subject Selection	12	Added "Positive for SARS-COV-2 at time of surgery" to exclusion criteria.
8 / July 5, 2023	Trial Summary/Abstract	7	Adjusted sample size and power estimation to reflect modified enrollment target
8 / July 5, 2023	Biostatistical Analysis Plan	30	Adjusted sample size and power estimation to reflect modified enrollment target

II) TRIAL SUMMARY / ABSTRACT

Study Title: Trial of Novel Oral Anticoagulants vs. Warfarin in New Onset Atrial Fibrillation after Cardiac Surgery (The NEW-AF study)

Background: New onset atrial fibrillation (NOAF) is a common occurrence following cardiac operations, occurring in anywhere from 20 to 50% of patients following cardiac operations. For patients with no prior history of arrhythmia who develop new onset, persistent atrial fibrillation after cardiac operations, the standard of care is combined pharmacologic therapy for rate control and prophylaxis against arterial thromboembolism, with consideration for rhythm control interventions where appropriate. Vitamin K antagonist therapy with Warfarin, the drug of choice for prophylaxis against stroke and systemic arterial thromboembolism comes with many challenges related to length of titration, monitoring requirements and bleeding risks. Novel anticoagulants like rivaroxaban may mitigate these limitations in this population of patients.

Study Design: Prospective, randomized, active-controlled, parallel arm study to compare the postoperative length of stay for patients who receive thromboembolism prophylaxis with Warfarin (active-control) vs. Rivaroxaban (A novel oral anticoagulants) for management of new onset atrial fibrillation after sternotomy for cardiac operations.

Study Hypotheses:

- Compared with Warfarin, Rivaroxaban will allow for earlier hospital discharge for patients who develop new onset atrial fibrillation after cardiac surgery
- Compared with Warfarin, Rivaroxaban will provide equally safe and efficacious prophylaxis against arterial and venous thromboembolism in patients who develop new onset atrial fibrillation after cardiac surgery

Inclusion Criteria for Enrollment:

- Male or Female ≥ 18 years
- One of the following procedures: coronary artery bypass grafting, aortic valve repair, mitral valve repair (including minimally invasive procedures), non-mechanical aortic valve replacement, ascending aorta or aortic root replacement, and any combination of these procedures
- Two or more episodes of NOAF (each lasting > 20 minutes) or persistent AF lasting > 24 hours (Or for >18 hours over a 24-hour interval)
- If female of child-bearing age, use of adequate contraception

Exclusion Criteria for Enrollment:

- Pre-existing paroxysmal atrial fibrillation before cardiac surgery
- Pre-existing indications for therapeutic anticoagulation (Including but not limited to PE, DVT, mechanical valve)
- Moderate-to-severe mitral valve stenosis not surgically corrected
- Pre-existing allergy to study medications
- Recent (< 1 year) or ongoing pregnancy (Urine pregnancy test will be obtained for women of child bearing age at the time of enrollment into the study)
- Stroke within 1 month prior to surgery or postoperatively prior to initiation of study drugs
- Postoperative bleeding episode prior to initiation of study drug
- Severe dysfunction of another organ system including GFR < 30 ml/min, baseline INR > 1.7, ileus or other gastrointestinal pathology hindering ability to absorb oral medications, and known coagulation pathway deficiencies
- Postoperative need for non-aspirin anti-platelet therapy that cannot be discontinued when therapeutic anticoagulation is initiated
- Patient taking medications with known major interactions with study drugs with no therapeutic alternatives
- Patient testing positive for SARS-COV-2 at time of surgery or during the post-operative period.

Criteria for Randomization:

- Persistent Atrial Fibrillation: Greater than 24 hours of continuous or near-continuous atrial fibrillation (>18 hours over a 24-hour period)
- Recurrent Atrial Fibrillation: 2nd or greater episode of atrial fibrillation, each lasting greater than 20 minutes

Intervention Arms:

1) Warfarin: Vitamin K antagonist requiring regular laboratory monitoring (INR) to determine adequacy of therapy
2) Rivaroxaban: Direct oral anticoagulant without routine monitoring requirements

Primary Outcomes:

- Length of stay (in days) from time of departure from the operating room following the index cardiac operation.
- Length of stay (in days) from time of initiation of therapeutic anticoagulation

Secondary Outcomes:

- Stroke or other arterial thrombo-embolism at 30 days from the index operation
- Development of major bleeding (Reoperation or other therapeutic intervention for bleeding, development of any intra-cranial bleeding, cessation of study drug, reversal of study drug for bleeding concerns and/or new transfusion requirement > 2 units of blood after drug administration)
- Deep venous thrombosis and pulmonary embolism at 30 days from the index operation
- Therapy related costs of anticoagulation
- Minor bleeding (Blood transfusions <= 2 units or drop in hgb > 3 g/dL after drug administration)
- Number of transfusions per group after initiation of study drugs
- Quality of Life Scores upon discharge from the hospital
- Heart Rhythm at discharge and at postoperative follow up in clinic
- Death

Power and Sample Size Estimations:

Sample size calculations will generate adequate power to detect meaningful differences in length of stay between the two study arms. Prior retrospective studies in the field are used to estimate parameters for calculations.

Anticipating a length of stay difference of 2 day between the study groups with standard deviation of 6 days in each group, it is estimated that a 2-sided confidence interval of 0.05 with power 80% will be generated with a sample size of 266 patients (133 per group). Estimating 10-15% attrition and/or cross-over over the course of the study, investigators originally aimed to enroll ~300 patients for study completion. Due to slow rates of recruitment beyond the control of the study team, the modified enrollment target is 100 patients for study completion with power ~65%.

Follow-up:

- Follow up for adverse events will continue until 30 days post cardiac surgery
- Patients will follow up with their cardiac surgeon and cardiologist within 30 days of cardiac surgery
- Enrolled patients will receive weekly phone calls with administration of a quality of life questionnaire two weeks after surgery

Estimated Study Length: Expected duration of this study from randomization of the first patient to the last exit interview / last phone call for the last patient is 36 months.

III) ABBREVIATIONS, ACRONYMS, DEFINITIONS

AF – Atrial Fibrillation
AKI – Acute Kidney Injury
AMS – Anticoagulation Management Service
AVR – Aortic Valve Replacement
CABG – Coronary Artery Bypass Grafting
CBC – Complete Blood Count
CMP – Comprehensive Metabolic Panel
CVA – Cerebrovascular Accident
DVT – Deep Venous Thrombosis
ECMO – Extracorporeal membrane oxygenation
EKG – Electrocardiogram
FDA – U.S. Food and Drug Administration
FFP – Fresh Frozen Plasma
GFR – Glomerular Filtration Rate
HCP – Health Care Proxy
IABP – Intra-aortic balloon pump
INR – International Normalized Ratio
IRB – Internal Review Board
LOS – Length of Stay
MGH – Massachusetts General Hospital
NOAC – New Oral Anticoagulant
NOAF – New Onset Atrial Fibrillation
NP – Nurse Practitioner
NSAID – Non-steroidal anti-inflammatory drug
PA – Physician Assistant
PCC - Prothrombin complex concentration
PE – Pulmonary Embolism
PHI – Protected Health Information
PI – Principal Investigator
PT – Prothrombin Time
PTT – Partial Thromboplastin Time
TIA – Transient Ischemic Attack

IV) BACKGROUND AND SIGNIFICANCE

HISTORICAL BACKGROUND

New onset atrial fibrillation (NOAF) is a common occurrence following cardiac operations, occurring in anywhere from 20 to 30% of patients following coronary artery bypass grafting (CABG) [Anderson et al., Am J Surg. 2015] and in up to 50% of patients undergoing cardiac valve operations [Lomivorotov et al. J Cardiothor and Vasc Anest. 2016]. The occurrence of postoperative atrial fibrillation has been linked with increased mortality compared with patients who do not develop new onset atrial fibrillation (NOAF) following cardiac operations [Megens et al. J Am Heart Assoc. 2017; Ahlsson et al. EJCTS. 2010; Galdine et al. JAMA. 2014]. For patients with no prior history of arrhythmia who develop persistent NOAF following cardiac operations, the standard of care includes pharmacological and procedural interventions to provide rhythm control or combined pharmacological therapies for rate control and prophylaxis against arterial thromboembolism. Recommendations from the American Heart Association and American College of Cardiology for patients who continue to have NOAF 48 hours after surgery are for rate control with a beta-blocker and arterial thromboembolism prophylaxis with an oral medication [2011 ACC/AHA/HRS Guidelines].

Historically, Vitamin K antagonist therapy with Warfarin has been the treatment of choice for prophylaxis against stroke and systemic arterial thromboembolism in NOAF, because it is the most extensively studied oral anticoagulant available. However, Warfarin therapy comes with many challenges including prolonged titration, tedious monitoring requirements and in some cases, increased bleeding risk [Charlton et al. Plos One. 2018; Anderson et al. Am J Surg 2015]. Patient satisfaction with this drug is also affected by dietary precautions that must be taken to maintain a steady International Normalized Ratio (INR) on a given dose of Warfarin. These limitations may be mitigated by using new oral anticoagulants (NOACs) like Rivaroxaban which have no routine monitoring requirements and may be just as effective as warfarin.

PREVIOUS STUDIES

Notable randomized studies like the ROCKET AF Trial (Rivaroxaban vs. Warfarin), the ARISTOTLE Trial (Apixaban vs. Warfarin), and the RELY Trial (Dabigatran vs. Warfarin) have demonstrated non-inferiority of NOACs compared with Warfarin for stroke prophylaxis in non-operative patients with atrial fibrillation [Connolly et al. NEJM. 2009; Granger et al. NEJM. 2011; Patel et al. NEJM. 2011]. Furthermore, these studies have demonstrated equivalent or lower rates of major peri-procedural bleeding for NOACs compared with warfarin [Healey. Circulation. 2012]. No prospective studies have been conducted to compare these drug classes in patients who have recently undergone cardiac surgical operations, however a recent retrospective analysis comparing NOACs with Warfarin in 598 patients who had recently undergone coronary artery bypass grafting (CABG) demonstrated no difference in clinical outcomes between the two treatments [Anderson et al. Am J Surg. 2015]. Notably, this study demonstrated lower overall drug related costs and shorter times to therapeutic anticoagulation and hospital discharge for patients on NOACs compared with those on Warfarin.

Anecdotally, one major concern with using NOACs following cardiac operations has been the absence of effective reversal agents for these drugs. In the setting of bleeding, Warfarin can be reversed quickly with Vitamin K and Fresh Frozen Plasma (FFP). These agents are not effective for reversing bleeding in patients on NOACs. However recent FDA approval of multiple agents for reversal of NOACS including Idarucizumab

(Dabigatran) and Andexanet Alfa (Rivaroxaban and Apixaban) should allay some of these concerns. Both Idarucizumab and Andexanet Alfa have been shown to decrease circulating levels of active forms of NOACS by up to 79% with evidence of good or excellent clinical hemostasis in almost 80% of patients [Pollack et al. NEJM. 2015; Siegal et al. NEJM. 2015; Connolly et al. NEJM. 2016].

RATIONALE FOR STUDY AND POTENTIAL BENEFITS

Considering the above described clinical evidence, there is clearly an opportunity to improve the quality of care provided to cardiac surgery patients who develop persistent and/or recurrent atrial fibrillation in the post-operative period. Our comprehensive heart center teams have equipoise for investigating this topic in prospective, randomized fashion.

Findings from this study could have significant implications in terms of cost of care and patient convenience following cardiac operations, even after discharge from the hospital. Should there be any differences in study safety outcomes, study data will provide guidance to make evidence driven decisions about choice of therapeutic agents in patients with NOAF.

V) SPECIFIC AIMS

PRIMARY OBJECTIVE

- The primary study aim is to compare postoperative length of stay with Rivaroxaban use (a new oral anticoagulant) versus Warfarin use (Standard of Care with target INR 2.0 – 3.0) in patients who develop persistent or recurrent new onset atrial fibrillation following cardiac surgery

SECONDARY OBJECTIVES

- The secondary study aim is to compare the efficacy (Measured as rates of arterial and venous thromboembolism prevention), safety (Measured as rate of major and minor bleeding, number of units transfused and rate of occurrence of significant postoperative adverse events) and therapy related financial costs of Rivaroxaban versus Warfarin for prophylaxis against thrombo-embolic events in patients who develop persistent or recurrent new onset atrial fibrillation following cardiac surgery
- An additional study aim is to compare quality of life scores with Rivaroxaban compared with Warfarin in patients who develop persistent or recurrent new onset atrial fibrillation after cardiac surgery

PRIMARY HYPOTHESIS

- Compared with Warfarin, Rivaroxaban will allow for earlier hospital discharge for patients who develop persistent or recurrent new onset atrial fibrillation after cardiac surgery

SECONDARY HYPOTHESIS

- Compared with Warfarin, Rivaroxaban will provide equally safe and efficacious prophylaxis against stroke and systemic thrombo-embolic events in patients who develop persistent or recurrent new onset atrial fibrillation after cardiac surgery
- Patients who develop persistent or recurrent new onset atrial fibrillation following cardiac surgery with have higher quality of life scores when managed with Rivaroxaban compared with Warfarin

VI) SUBJECT SELECTION

This is a prospective, randomized, controlled study to compare length of stay, safety and financial benefits of stroke and systemic arterial thromboembolism prophylaxis with Warfarin vs. Rivaroxaban in patients with new onset atrial fibrillation (NOAF) after sternotomy for coronary artery bypass operations (CABG), aortic valve repair, non-mechanical aortic valve replacement, mitral valve repair (including minimally invasive procedures), ascending aorta or aortic root replacement, and combined procedures involving combination of these aforementioned procedures. Prior to randomization, inclusion and exclusion criteria for each potential participant will be documented carefully and confirmed with a study PI.

INCLUSION CRITERIA

- Male or Female ≥ 18 years
- At least one of the following procedures: coronary artery bypass grafting, aortic valve repair, mitral valve repair (including minimally invasive procedures), non-mechanical aortic valve replacement, ascending aorta or aortic root replacement, any combination of these procedures
- Two or more episodes of NOAF (each lasting > 20 minutes) or persistent AF lasting > 24 hours (Or for >18 hours over a 24-hour interval)
- If female of child-bearing age, use of adequate contraception

EXCLUSION CRITERIA

- Pre-existing paroxysmal atrial fibrillation before cardiac surgery
- Pre-existing indications for therapeutic anticoagulation (Including but not limited to PE, DVT, mechanical valve)
- Moderate-to-severe mitral valve stenosis not surgically corrected
- Pre-existing allergy to study medications
- Recent (< 1 year) or ongoing pregnancy (Urine pregnancy test will be obtained for women of child bearing age at the time of enrollment into the study)
- Stroke within 1 month prior to surgery or postoperatively prior to initiation of study drugs
- Postoperative bleeding episode prior to initiation of study drug
- Severe dysfunction of another organ system including GFR < 30 ml/min, baseline INR > 1.7, ileus or other gastrointestinal pathology hindering ability to absorb oral medications, and known coagulation pathway deficiencies
- Postoperative need for non-aspirin anti-platelet therapy that cannot be discontinued when therapeutic anticoagulation is initiated

- Patient taking medications with known major interactions with study drugs with no therapeutic alternatives)
- Patient testing positive for SARS-COV-2 at time of surgery or during the post-operative period.

RECRUITMENT METHODS AND SOURCE OF SUBJECTS

The pool of potential study participants will include all recipients of cardiac surgery operations at Massachusetts General Hospital. Estimates from prior studies suggest at least a 20% incidence of atrial fibrillation following cardiac surgery operations. The numbers will be similar in our pool of potential study participants. To supplement our data, we may utilize data from other similar studies that have completed.

The annual case volume at MGH of the study specific cardiac operations is approximately 750 cases. The 20% incidence of atrial fibrillation will yield an enrollment cohort of approximately 150 patients annually. Estimating a 50% progression to persistent or recurrent atrial fibrillation, and a 10% rate of refusal to participate in the study, approximately 65 patients will be randomized every year. Recruitment of patients in this study will not be affected by patient gender, ethnicity, culture or language. Demographic data will be collected for randomized patients to monitor trends in study recruitment based on these factors.

Patients scheduled to undergo the relevant cardiac operations will receive study materials including fliers describing the study interventions, potential benefits (individual and societal), and potential risks of the study. At this stage, providers involved in the patient's care (surgeons, cardiologist, nurse practitioners [NPs], physician assistants [PAs]) will be asked to discuss the study with their patients to gauge interest in participation. These initial conversations will happen during outpatient visits in clinics, and in the inpatient setting for operations that are scheduled while patients are admitted. Providers will be made aware of the study using email communications, meetings with staff (including unit coordinators and nursing staff), and fliers posted in strategic positions in target locations both in the outpatient and inpatient settings.

Following their cardiac surgery operations, patients who develop new onset atrial fibrillation will be identified based on daily conversations with inpatient providers including physicians, NPs, PAs and registered nurses. After discussions with providers, and receipt of permission from patients, study staff will approach potential participants and provide them with the consent forms and additional copies of recruitment materials. Informed consent will not be obtained at this time.

Patients who go on to develop recurrent or persistent atrial fibrillation will be approached again by study staff to discuss the study in detail. At this juncture, patients who agree to participate in the study will go through the detailed informed consent process and be randomized to one of the two study arms.

Principal investigators will evaluate study enrollment rates twice monthly to understand patterns of enrollment against estimated numbers. Additional strategies to improve study enrollment will be adopted as needed.

VII) ENDPOINTS

PRIMARY ENDPOINT

The primary efficacy outcome for this study will be length of stay in days from time of departure from the operating room following the index cardiac operation. Estimations will be made to the nearest quarter of a day with the starting time defined as the time of departure from the operating room, and the discharge time defined as the time the discharge summary is signed.

Adjusted length of stay will be calculated to account for time patients spend in the hospital during readmission encounters, both at our hospital and at other medical centers. Patient who present to the emergency department but do not get admitted to the hospital will have one day added to the adjusted length of stay for each separate emergency department visit. Scheduled and un-scheduled outpatient visits will not lead to accrual of additional time toward adjusted length of stay.

SECONDARY STUDY ENDPOINTS

Several additional endpoints will be estimated for study participants as outline below:

- **Major Bleeding:** A safety outcome for this study will be the occurrence of major bleeding in patients randomized to study drugs. For study purposes, major bleeding will be defined as reoperation or other therapeutic intervention for bleeding (including but not limited to colonoscopy, upper endoscopy and urologic procedures for hematuria), development of any intra-cranial bleeding, cessation of study drug for bleeding concerns, reversal of study drug for bleeding concerns and/or new transfusion requirement > 2 units of blood after drug administration. Rates of major bleeding will be compared between the two intervention groups.

- **Cerebrovascular Accident:** Rates of cerebrovascular accident including stroke and transient ischemic attack (TIA) will be compared across intervention groups. Suspected cerebrovascular accidents (CVA) based on physical exam findings of new focal or generalized neurologic deficits will be confirmed by a board-certified neurologist with appropriate work up, including imaging and administration of comprehensive neurological examination. Distinctions will be made between stroke (characterized by deficits lasting > 24 hours and/or imaging findings of infarction) and TIA (characterized by examination findings lasting < 24 hours without associated imaging findings). Distinctions will also be made between hemorrhagic and ischemic etiologies for CVA.

- **Other Arterial Thromboembolism:** Occurrence of non-neurological systemic arterial embolism involving any organ system will be compared across study intervention groups. These will generally be diagnosed by imaging after laboratory or physical exam findings suggest pathology.

- **Venous thrombo-embolism (Deep Venous Thrombosis [DVT] and Pulmonary Embolism [PE]):** Occurrence of pathologic venous thrombo-embolism including DVT and PE will be compared between the intervention arms. Diagnosis will be made by imaging evaluation obtained in the appropriate clinical setting.

- **Minor Bleeding:** Rates of minor bleeding will be compared between the two study intervention arms. Minor bleeding will be defined for study participants as blood transfusions <= 2 units or

drop in hemoglobin greater 3g/dL following randomization and administration or either study drug.

- **Number of Transfusions:** In addition to the estimations of major and minor bleeding as outlined previously, the number of units of blood transfused for each participant after initiation of study drugs will be compiled. Average number of units transfused per patient will be compared between the two study intervention groups

- **Readmission:** Rates of hospital readmission will be estimated for patients in each of the study intervention groups. Readmissions will be counted in this calculation if patients are admitted to the hospital. Emergency room visits without admission and outpatient visits will not count toward this calculation of readmission rates.

- **Therapy Related Costs of anticoagulation**: Specific drug related costs will be estimated in dollars for patients in each intervention arm. For Rivaroxaban, this will include the cost of the drug based on daily dosing for the duration of the study. For Warfarin, this will include the cost of the drug based on daily dosing for the duration of the study, as well as mileage-based cost of transportation to INR testing location, and cost of each INR test obtained in the outpatient setting. Length of stay, readmissions and clinical complications will not be considered in this cost calculation.

- **Scores on Quality of Life Surveys**: Two to six weeks following hospital discharge, patients will be administered a quality of life questionnaire incorporating elements of the EQ-5D-3L Health Questionnaire and the Perception Anticoagulant Treatment Questionnaire (PACT-Q2) either by phone or in person, depending on the timing of their postoperative visit. Scores from this questionnaire will be estimated for each patient and compared between the two study groups.

- **Rhythm Related Outcomes:** Patient enrolled in the study will remain on cardiac monitors through the duration of their hospital stay per standard of care at our center. EKGs will be obtained at the time of diagnosis of AF, and at the time of discharge from the hospital. Additional EKGs will be obtained at the cardiac surgery clinic visit (On average five weeks following discharge) and at cardiology clinic visit (On average four weeks following discharge) to document cardiac rhythm at these various time points. For patients who do not have EKGs within the last week prior to study completion, an EKG will be obtained at the exit visit. Related secondary outcomes will include data on continuation of anticoagulation at the end of study enrollment and choice of drug for anticoagulation. Decisions for continuation of anticoagulation and choice of drug will be made by the patient's cardiologist based on cardiac rhythm and individual risk-benefit consideration for each participant.

- **Study specific length of stay:** Additional length of stay calculations will include calculations of study specific length of stay which will be comprised of the time from initiation of therapeutic anticoagulation with Warfarin or Rivaroxaban to the time of study specific eligibility for discharge from the hospital. Criteria for study specific discharge eligibility will include achieving therapeutic INR (for warfarin) and receiving two doses of Rivaroxaban without clinical or laboratory concern for major or minor bleeding (both previously defined), or any other drug related adverse event. This study specific length of stay will be calculated irrespective of time of actual physical departure from the hospital.

- **Death:** Death within the study dates will be compared across the two study intervention groups. Cause of death will be documented for all participants who die during the study.

- **Other Adverse Events:** Through the course of enrollment, patients will be monitored for occurrence of adverse events related to organ systems not listed thus far in the proposal. For purpose of these study "other adverse event" will refer to a clinical occurrence that affects patient recovery, requires specific monitoring and/or management, prolongs hospitalization, leads to disability or leads to fatality. These adverse events will be compared between study intervention arms and will include (but not be limited to):

    - ***Acute Kidney Injury (AKI):*** AKI will be defined as doubling of creatinine levels from pre-randomization levels or decrease in glomerular filtration rate by >= 50%. Progression to renal failure will be recorded and defined as decrease in glomerular filtration rate <15ml/min, increase in serum creatinine >= 4mg/dL and/or need for renal replacement therapy in the form of hemodialysis or continuous veno-venous hemofiltration. Suspicion for AKI or renal failure will be confirmed by and managed in conjunction with a board-certified nephrologist

    - ***Infection:*** Infection during the post-operative period including but not limited to those involving the surgical site, cardio vascular system, respiratory system, genito-urinary system or hematologic system will be documented and compared between intervention arms. These infections will be diagnosed based on appropriate imaging and laboratory evidence, obtained in the appropriate clinical context. Infections will be managed per standard of care at our center. Notification will be made of the infectious diagnosis and management employed by the clinical team.

    - ***Heart Failure:*** Clinical, laboratory or imaging evidence of heart failure with documentation of this diagnosis in the clinical chart by a board-certified cardiologist will be compared between intervention arms.

    - ***Pericardial Effusion:*** Clinically significant fluid accumulation in the sack surrounding the heart (the pericardium), requiring additional diuresis and/or interventions for drainage will be compared between intervention arms.

    - ***Myocardial Infarction:*** Myocardial infarction diagnosed based on EKG and laboratory testing including pursued intervention and/or findings from subsequent angiography will be compared between intervention groups. To be considered a myocardial infarction, the diagnosis will have to be confirmed and documented in the chart by a board-certified cardiologist.

    - ***Pleural Effusion:*** Clinically significant fluid accumulation in either or both pleural cavities requiring additional diuresis and/or intervention for drainage will be compared between intervention arms.

    - ***Hepatic Dysfunction:*** Liver dysfunction characterized by increase in parameters of liver function tests greater than four-fold from pre-randomization levels, evidence of progressive hepatobiliary pathology on imaging and/or consultation with a board certified hepatologist will be documented and compared between intervention arms.

VIII) SUBJECT ENROLLMENT

ENROLLMENT METHODS AND REGISTRATION

Patients scheduled for cardiac surgery at our center, either from cardiac surgery clinics, or in the inpatient wards will be provided with general information about the study. No enrollment or randomization will take place in this pre-operative period.

Patients who develop atrial fibrillation in the inpatient setting following sternotomy for the previously outlined cardiac surgery operations will be approached and provided with information about the study protocol. Providers will discuss the study with potential participants prior to conversations with study staff. Patients who are interested in speaking with study staff, and who satisfy study criteria (for inclusion and exclusion) will be screened via in-person interview and provided with consent forms and study materials. Written consent for the study will not be obtained at this time. However, initial conversations will be detailed, and will be initiated as soon after the onset of atrial fibrillation as possible to give potential participants ample time between screening and consenting/randomization to consider involvement in the trial.

At this juncture demographic, medical and operative information for each potential study participant will be assessed, but no study treatments will be administered. Risk to patients at this stage will be minimal and limited to risks in the domain of protected health information (PHI) management. As outlined elsewhere, strategies will be implemented to maintain anonymity and keep PHI safe. Each patient will be assigned a unique identification code that will accompany all documentation and analysis throughout the course of the study.

RANDOMIZATION AND TREATMENT ASSIGNMENT

Each patient who has screened and subsequently meets criteria for recurrent atrial fibrillation (>= two episodes, each lasting >= 20 minutes) or persistent atrial fibrillation (continuous or near continuous atrial fibrillation for 24 hours) will be approached by study staff. A thorough discussion about the study including protocols, risks and benefits of the study, participant rights and follow up plan will be initiated, and informed consent will be obtained. Ample time will be provided for potential participants to ask questions about any details of the study. The process for informed consent will be detailed carefully in study records. Following provision of written consent, participants will be randomized by study staff into one of two study treatment arms:

Intervention 1: Warfarin therapy for anticoagulation (Standard of care with goal INR 2.0-3.0)
Intervention 2: Rivaroxaban therapy for anticoagulation (No INR goals)

Standard of care for patients with persistent or recurrent new onset atrial fibrillation is rate control with nodal blocking agents and therapeutic anticoagulation, usually with warfarin. Patients randomized in this trial will vary from standard of care only in the possibility of receiving a different medication for therapeutic anticoagulation. The criteria for persistent and recurrent atrial fibrillation were selected based on usual pathways for post-operative care at our center.

Patients assigned to a given treatment group will be expected to complete the study in their assigned group. Crossover will be permitted if there are any adverse events or other factors that preclude use of a

particular study drug for a given patient. Analyses will be performed in intention-to-treat fashion with complementary per-protocol calculations to highlight the effect of crossover.

The sequence of randomization will be predetermined using random number generation from statistical analysis software. Allocation will thus be pre-determined (prior to study initiation) as it relates to sequence of participant entry into the study. Allocation into either study group will not be concealed from the participants, providers or study staff.

PROCEDURES FOR AND TIMING OF INFORMED CONSENT

Informed consent will be obtained for randomization into one of the study intervention groups at the time that a patient meets criteria for recurrent or persistent new onset atrial fibrillation. Inclusion will be limited to occurrence of NOAF during the index hospitalization after a cardiac surgical procedure. Informed consent will generally be obtained on the inpatient floor, in post-operative step down or in the intensive care unit following cardiac surgical operations. In general EKGs or other rhythm assessments are not performed on routine follow up patients who are seen in cardiac surgery clinic. It is thus unlikely that any cases of asymptomatic new onset atrial fibrillation will be discovered in patients who are discharged from the hospital without an arrhythmia. As patient who initially developed atrial fibrillation will already have been approached by study staff prior to development of persistent or recurrent arrhythmia (and registered in the screening cohort), potential participants will already have been provided with informational materials about the study. Participants will thus be afforded adequate time to consider involvement in the study.

Informed consent will be obtained by licensed physician investigators with support from study research nurses and clinical research coordinators. The consent process will include a full review of the consent paperwork, thorough discussions about risks, benefits and participant rights, and provision of ample time for potential participants to ask questions about the trial. The consent process will be documented for each interaction and written consent will be obtained from interested participants.

Consent for Special Populations

Patients who do not speak English as their primary language will also be afforded the opportunity to participate in the study. In these cases, the consent process will occur via a professionally trained and certified interpreter (Preferably in person using hospital interpretation services, but possibly using contracted phone or video-based interpreter services). The patient will still be asked to sign the English version of the consent form, but this will be supplemented with a Partners Healthcare certified short form consent in the patient's primary language. Both the patient and interpreter will be required to sign this short form.

Patients without mental capacity to consent will not be included in the study.

Withdrawal of Consent

Study participants may withdraw consent at any time during the study. In the event of withdrawal of consent, study participation will immediately cease, and care will return to standard of care as guided by the patient's providers. Any requirements for transition of care including bridging anticoagulation and education for new treatment will be facilitated by study personnel. An exit interview will be conducted with patients at the time of withdrawal from the study, preferably in person, but potentially by phone if within 3 days from outpatient visits with cardiology or cardiac surgery.

Study data will be collected in a continuous fashion throughout the study and investigators will reserve the right to include data gathered up to the point of withdrawal in study analyses. Furthermore, investigator may collect future outcome data based on chart review and conversations with patients, even after withdrawal from the study, unless explicitly forbidden by the participant. The value of such ongoing review cannot be emphasized enough particularly if the patient withdraws following an adverse event. Follow up of such events is an integral part of ensuring optimal patient management (up till resolution of events), and a critical part of the trial protocol which will help to minimize the risk of unrecognized recurrent complications.

IX) STUDY PROCEDURES AND DESIGN

STUDY VISITS AND PARAMETERS

The followings study visits will be conducted for study participants with data collection as detailed:

- **Clinic visit and Inpatient Consultation**
  Patients who are scheduled for any of the cardiac surgical operations that meet study inclusion criteria will be provided with fliers describing the study in detail. Patients will be informed that this is a study that they could be potentially eligible for in the postoperative period.

- **Initial screening visit at the time of development of atrial fibrillation following cardiac surgery**
  Patients who develop atrial fibrillation after their cardiac operations will be approached to discuss the study and provided with study informational materials. Patients will not be consented at this time. Data assessed will include demographic information (gender, ethnicity, date of birth and primary language), history relating to major comorbidities and active medications, operating room history (date of surgery, time of departure from the operating room and procedures performed), and peri-operative history (including major adverse events).

- **Randomization**
  At the time of development of recurrent or persistent atrial fibrillation, patients who meet study criteria will be approached to participate in the intervention phase of the study. Those who agree to participate and sign informed consent will be randomized at this point to one or the other study intervention. Baseline data collected will include EKG rhythm, average HR over the preceding 24 hours, rate and rhythm control interventions to date, and laboratory values including complete blood count (CBC), comprehensive metabolic panel (CMP), and International Normalized Ratio (INR). Laboratory values and EKGs are obtained as part of routine care. These tests will not represent a deviation from the standard protocol following cardiac surgery.

- **Inpatient Monitoring**
  Following randomization, patient care will continue per standard at our center. During the course of the inpatient admission, study personnel will follow enrollees closely to monitor laboratory values, adverse events (including reactions or complications related to study drugs) and ongoing pharmacologic interventions for rate and rhythm control

- **Discharge**

Patients will be discharged when they meet typical criteria for discharge as determined by the inpatient providers taking care of them. At the time of discharge from the hospital, study staff will re-visit study details with enrollees, emphasizing ongoing enrollment in the trial, complications to watch out for, plans for ongoing follow up including by phone and in clinic, rights of study participants, and details about how to contact investigators to discuss any parts of the study. An EKG and a set of laboratory values will be collected in the morning on the day of discharge including a CBC, CMP and INR. Additional data related to discharge will be collected including patient contact information, time of signing of discharge order, discharge destination (home vs. rehabilitation center), scheduled follow up appointments (Including dates and locations of clinics and INR monitoring facilities), and data on atrial fibrillation interventions at the time of discharge including rate/rhythm control agents, and agent used for therapeutic anticoagulation.

- **Phone Call Week 1-2**
  One to two weeks from the date of discharge, patients will receive a phone call from study staff. This brief, structured phone call will explore general recovery post-discharge, ongoing participation in rehabilitation and physical therapy, and number of outpatient visits for INR checks (for patients in the warfarin arm). Patients whose INR values are not obtained at a Partners facility will be asked to share their INR values with study staff. A quality of life questionnaire will be administered. Time will be provided for participants to ask questions about the study.

- **Cardiology Clinic Visit**
  Follow up with cardiologists will occur three to four weeks after discharge. This visit will generally involve performance of an EKG and decision making about ongoing therapeutic anticoagulation based on EKG findings. For patients who have cardiologists who see patient at the MGH main campus, study staff will conduct in person interviews to discuss recovery, complications and INR follow up. Data on cardiac rhythm and plans for therapeutic anticoagulation (as determined by the cardiologists) will be collected by study staff. Pill diaries will also be reviewed. For patients who follow up with their cardiologists at a location other than the MGH main campus, study staff will call the cardiology office a few days following the cardiology outpatient visit to obtain data on cardiac rhythm and plans for therapeutic anticoagulation. In the event that ongoing therapeutic anticoagulation is required for persistent atrial fibrillation, and the decision is made at this visit by the patient and cardiologist to switch therapies from Rivaroxaban to Warfarin, the transition to an anticoagulation monitoring service (at the anticoagulation clinic, with their PCP or with their cardiologist) will be facilitated by study staff and clinical providers from cardiology and cardiac surgery. Whether or not therapies are switched, the patients' ongoing anticoagulation follow up and titration will be transitioned at the time of study exit to their primary cardiologist.

- **Cardiac Surgery Clinic Visit / Exit Interview**
  The routine post-operative visit following cardiac operations will occur approximately five weeks after discharge. At this visit, study staff will meet with participants. Data will be gathered on general recovery at home, frequency of INR monitoring visits and ongoing participation in rehabilitation and physical therapy. Adherence will be assessed via evaluation of patient pill diaries. The atrial fibrillation quality of life questionnaire will be administered if not already completed. At this visit, study staff will review complications and overall recovery following cardiac operations, final anticoagulation plan and final length of stay calculations. EKG will be obtained (If not obtained within the preceding 5 days). Patients will be given the opportunity to ask questions and provided with contact information for study investigators.

STUDY DRUGS (DOSE, METHOD, SCHEDULE, MODIFICATIONS AND TOXICITY +/- GRADING SCALE)

Overall Management

The management of patient with new onset atrial fibrillation will be conducted per standard of care at our center. This will include treatment of potential underlying etiologies including, but not limited to fluid imbalance, electrolyte abnormalities, hypoxemia, chemical stimulation (alpha agonists including bronchodilators and inotropes) and fever. Other therapies for rate and/or rhythm control will be administered at the discretion of the participant's primary team and will not be affected by enrollment in the study.

Warfarin (Also Coumadin)

Mechanism of Action and Indications

Warfarin is a competitive inhibitor of vitamin K epoxide reductase complex 1, an important enzyme in the activation pathway for vitamin K dependent coagulation factors. By inhibiting the function of this enzyme, warfarin reduces the availability of the functional form of vitamin K, thus reducing the synthesis of active clotting factors and ultimately slowing down both intrinsic and extrinsic aspects of the clotting cascade.

Warfarin is FDA approved for prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and cardiac valve replacement.

Drug Administration Method

Warfarin will be administered by mouth to study participants. Patient who require intravenous warfarin will not be included in the study. Warfarin tablets come in multiple strengths providing flexibility for careful titration toward INR goals for each individual patient. Pill sizes include 1mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 6mg, 7.5mg and 10mg.

Drug Administration Schedule

Warfarin will be administered daily with recommendations for use at the same time every day, preferably in the evening after dinner.

Initial Dosing, modification and monitoring

Warfarin dosing will be selected at the discretion of the primary team, including decisions about initial dosing and maintenance based on INR monitoring. Per standard practice at our center, patients initiated on warfarin for atrial fibrillation will be bridged with intravenous unfractionated heparin until the INR reaches the therapeutic range. Frequency of PTT checks and goal PTT for bridged patients will be in accordance with center specific ranges for arterial thromboembolism prophylaxis. The following recommendations will be made for initial warfarin doses for patients enrolled in our study. Recommendations are based on instructions from the manufacturer:

- For patients with no underlying hepatic or renal dysfunction, and no known relevant genetic predispositions to warfarin sensitivity (or insensitivity), we will recommend an initial dose between **2-5mg taken by mouth every evening (after dinner)**. Choice of initial dose within this range will be made based on clinical factors including patient weight, age, gender, comorbidities, medications and anticipated maintenance dose

- For patients with underlying hepatic or renal disease, and/or known genetic mutations that affect warfarin metabolism, initial doses will be made based on guidelines from the medication package insert that accompanies this proposal.

Goal INR for patients enrolled in this study who are randomized to receive warfarin will be 2.0-3.0. INR will be monitored daily following administration of the initial dose until INR stabilizes within the therapeutic range. Titration will be performed by the primary team per existing standards at our center to achieve the target INR as efficiently and safely as possible. Following stabilization in the inpatient setting, INR will be checked at least every third day. Following discharge from the hospital, INR will be checked at least every other week with increase in frequency of checking when changes are made to other medications, when INR falls out of range and/or whenever clinically indicated based on signs and symptoms described by the patient. Patients who miss a dose of warfarin will be asked to take the dose as soon as possible that day. There will be strong recommendations against doubling dosing to make up for missed administrations.

Contraindications and Significant Toxicities
Warfarin is contraindicated for certain patient groups that will be excluded from this study. This includes pregnant patients, patients with known bleeding tendencies, patients with blood dyscrasias, patients with inability to maintain compliance (with medication use and monitoring), patients with malignant hypertension, and patients who have recently been victims of major trauma or recently undergone procedures involving the eye or central nervous system.

Toxicities from warfarin use are detailed in the "Risk and Discomforts" section of this proposal. Significant potential adverse effects worth highlighting here include major and minor bleeding, skin necrosis and systemic embolism of atheromatous plaques. Bleeding risk is especially high in patients with INR >4.0, age > 65, major hepatic, hematologic, renal or cardiac comorbidities, certain genetic factors and long duration of coumadin therapy. Patients at high bleeding risk will benefit from increased frequency of INR monitoring.

Drug Interactions
Several drugs may interfere with warfarin by affecting its activity and/or its metabolism. While concurrent use is not always contraindicated, it is important to recognize these drugs and perform INR monitoring more frequently when introducing or removing these drugs from a patient's medication regimen. A detailed, but non-exhaustive list of potential interactors is provided below. Many of these drugs are either known to increase bleeding risk or known to inhibit and/or induce the CYP450 isoenzyme, a protein that is intricately involved in the metabolism of warfarin. For patients enrolled in the study, every concurrent medication will be cross-checked against warfarin to discover potential interactions either directly with warfarin, or indirectly with the CYP450 enzyme or the clotting cascade. Discovered interactions will be managed with increased frequency of INR monitoring, therapeutic substitution where possible (provided there are no costs to the patient either financial or clinical) and exclusion from the study where there is no therapeutic alternative for a necessary medication whose use is contraindicated in conjunction with warfarin.

The attached warfarin packaging insert describes notable potential drug interactions including:

- ***CYP450 Inhibitors:*** Acyclovir, allopurinol, alprazolam, amiodarone, amlodipine, amprenavir, aprepitant, atorvastatin, atazanavir, bicalutamide, caffeine, capecitabine, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, cotrimoxazole, cyclosporin, darunavir, diltiazem,

disulfiram, enoxacin, etravirine, erythromycin, famotidine, fluconazole, fluoxetine, Fluvastatin, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lopinavir, methoxsalen, metronidazole, mexiletine, miconazole, nefazodone, nelfinavir, nilotinib, norfloxacin, oral contraceptives, oxandrolone, phenyl-propanoloamine, posaconazole, propafenone, propranolol, ranitidine, ranolazine, ritonavir, saquinavir, sulfinpyrazone, telithromycin, tipranavir, terbinafine, thiabendazole, ticlopidine, tigecycline, verapamil, voriconazole, zafirlukast, zileuton

- ***CYP450 Inducers:*** Amprenavir, aprepitant, armodafinil, bosentan, carbamazepine, efavirenz, etravirine, modafinil, montelukast, moricizine, nafcillin, omeprazole, phenobarbital, phenytoin, pioglitazone, prednisone, rifampin, rufinamide, tobacco

- ***Anticoagulants:*** Argatroban, apixaban, dabigatran, bivalirudin, desirudin, edoxabapn, heparin, lepirudin, rivaroxaban

- ***Antiplatelets:*** Aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine

- ***Nonsteroidal Anti-Inflammatory Agents (NSAIDS):*** Celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac

- ***Serotonin Reuptake Inhibitors***: Citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone

- ***Herbal products:*** Co-enzyme Q_{10}, echinacea, garlic, ginkgo biloba, ginseng, goldenseal, St. John's Wort

Reversal of Anticoagulant Effect
In the setting of active bleeding, the anticoagulation effect of warfarin is managed with discontinuation of warfarin therapy and reversal using oral or intravenous vitamin K therapy.

If urgent reversal is needed, FFP, prothrombin complex concentration (PCC) and recombinant factor VIIa can be used for reversal. Notably there is an increased risk of thrombosis with these agents, highlighting the need to use them only if there is concern for significant or life-threatening bleeding.

Rivaroxaban (Also Xarelto)

Mechanism of Action
Rivaroxaban is a direct inhibitor of Factor Xa. This enzyme (factor Xa) contributes to clotting by stimulating the formation of thrombin from prothrombin, a critical step in both the intrinsic and extrinsic aspects of the coagulation cascade. By inhibiting factor Xa, Rivaroxaban decreases both platelet activation and fibrin clot formation.

Rivaroxaban is FDA approved for prophylaxis against stroke and systemic embolism in patients with non-valvular atrial fibrillation. Although the distinction is not entirely agreed upon, non-valvular atrial fibrillation refers to AF in patients with no history of mitral stenosis or cardiac valve intervention (repair or replacement).

Drug Administration Method
Rivaroxaban will be administered by mouth to study participants. The tablet comes in 10mg, 15mg and 20mg forms. These tablets may be crushed and taken immediately with applesauce if patients are unable to swallow whole pills.

Drug Administration Schedule
Rivaroxaban will be administered once daily with the evening meal.

Initial Dosing, modification and monitoring
Rivaroxaban will be dosed in this study as outlined below per recommendations from the manufacturer. There will be no bridging therapy once treatment is initiated with Rivaroxaban.

- For patients with creatinine clearance or glomerular filtration rate (GFR) > 50 ml/min, Rivaroxaban will be dosed at **20mg taken by mouth every evening with the evening meal**

- For patients with creatinine clearance or GFR between 30 ml/min and 50 ml/min, Rivaroxaban will be dosed at **15mg taken by mouth every evening with the evening meal.**

There is no laboratory monitoring requirement for Rivaroxaban. Inpatients started on this treatment routinely have CBCs followed to monitor for bleeding. Patients who miss a dose of rivaroxaban will be asked to resume their regimen by taking their dose immediately (if discovered the day it was missed) or early the following day without doubling their total daily dose to make up for missed administrations.

Contraindications and Significant Toxicities
Rivaroxaban is contraindicated in patients with active bleeding or known hypersensitivity reactions to this drug. It is also contraindicated in patients with known bleeding tendencies or blood dyscrasias, patients with renal failure, patients with Child-Pugh B or worse hepatic dysfunction and patients who have recently been victims of major trauma or recently undergone procedures involving the eye or central nervous system. Rivaroxaban has not been studied in pregnancy. Pregnant patients will be excluded from enrollment in this study.

Toxicities from Rivaroxaban use are detailed in the “Risk and Discomforts” section of this proposal. Significant potential adverse effects worth highlighting here include major and minor bleeding, and increased risk of thrombotic events after discontinuation. This latter toxicity has been highlighted in prior trials with increased risk of stroke noted during the transition from Rivaroxaban to Warfarin. For this study patients crossing over from the Rivaroxaban to Warfarin trial arms will be bridged with unfractionated heparin administered intra-venously or low molecular weight heparin administered intramuscularly. In this specific scenario, bridging will be initiated 24 hours after discontinuation of rivaroxaban.

Drug Interactions
Several drugs may interfere with Rivaroxaban efficacy by affecting its activity and/or metabolism. While concurrent use is not always contraindicated, it is important to recognize these drugs and perform closer clinical and laboratory monitoring when introducing or removing these drugs from a patient’s medication regimen. Many of these drugs are either known to increase bleeding risk or interact with drug transport systems (Like P-pg and ATP-binding cassette), and enzymes that are essential for Rivaroxaban activity and metabolism. A detailed, but non-exhaustive list of potential interactors is provided below.

The attached Rivaroxaban packaging insert describes notable potential drug interactions including:

- ***CYP450 and drug transport system (P-gp, ATP binding Cassette) Inhibitors:*** Amiodarone, clarithromycin, diltiazem, dronedarone, erythromycin, fluconazole, ketoconazole, ritonavir, verapamil

- ***CYP450 and drug transport system (P-gp, ATP binding Cassette) Inducers***: Carbamazepine, phenytoin, rifampin, St. John's Wort

- ***Anticoagulants:*** Argatroban, apixaban, dabigatran, bivalirudin, desirudin, edoxabapn, heparin, lepirudin, rivaroxaban

- ***Antiplatelets***: Aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine

- ***Nonsteroidal Anti-Inflammatory Agents (NSAIDS):*** Celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac

Reversal of Anticoagulant Effect

In the setting of active bleeding, the anticoagulation effect of Rivaroxaban is reversible using the recently FDA approved drug Andexanet Alpha, a recombinant modified human factor Xa decoy protein. This drug works by competitive inhibition to decrease the effective circulating concentration of factor Xa inhibitors and was shown in studies to promote significantly higher rates of good or excellent clinical hemostasis in nearly 80% of patients. Studies tested patients who received this drug within 18 hours of their last dose of a factor Xa inhibitor. Andexanet Alpha was dosed in studies as a 400mg bolus followed by a 2-hour infusion at 480mg per hour.

Partial reversal of anticoagulant effect has been seen in healthy volunteers on Rivaroxaban who received PCC. This product may be used in the setting of life-threatening hemorrhage. Protamine sulfate, FFP, vitamin K, recombinant factor VIIa and hemodialysis have not been shown to decrease the anticoagulant effect of Rivaroxaban.

X) DATA COLLECTION AND MANAGEMENT

DATA COLLECTION SCHEDULE

DATA COLLECTION SCHEDULE								
ASSESSMENT	Onset of AF	Rec. /Pers. AF	Inpatient Trtmt.	Hosp. Discharge	Out-Patient	Phone Wk 1-2	Cardiology Clinic	Surgery Clinic (Exit)
General								
Eligibility and Registration	X							
Demographics	X							
Comorbidities / History	X							
Medications	X							
Operating Room History	X							
Perioperative Events	X							
Informed Consent		X						
Randomization into Treatment Groups		X						
Clinical Studies								
EKG / Tele		X	X	X			X	X
CBC, CMP, LFTs		X	X	X				
INR		X	X	X	X			
Ongoing Assessment								
HR Data		X					X	X
Rate & Rhythm Interventions		X	X	X			X	X
Inpatient Events / Procedures			X	X				
Secondary Outcomes			X	X	X	X	X	X
LOS Data				X				X
Rehab, Recovery and FU				X		X	X	X
Adverse Events			X	X	X	X	X	X
Adherence Data							X	X
AF QOL Assessments						X		X
Readmission Data					X	X		X
Anticoagulation Cost Data								X
Study Conclusion								
Final Anticoagulation Data							X	X
End of Study Reports								X
Abbreviations								
AF - Atrial fibrillation; Rec - Recurrent; Pers - Persistent; Trtmt - Treatment; Wk - Week; Tele - Telemetry; EKG - Electrocardiogram; CBC - Complete blood count; CMP - Comprehensive Metabollic Panel; LFT - Liver Function Labs; INR - International Normalized Ratio; HR - Heart Rate; LOS - Length of Stay; FU - Follow Up; QOL - Quality of Life								
Notes								
Recurrent AF - AF occuring on two or more occasions, each lasting > 20 minutes, within a 48 hour period								
Persistent AF - Continuous or Near continuous AF over a 24 hour period								

DATA MANAGEMENT PLAN

All study data will be collected using data collection sheets and stored electronically in password protected folders under the Partners Healthcare Network. Each patient will be assigned study numbers at registration and randomization which will be used for any data transfer to statistical software or databases outside the Partners Network. All protected health information (PHI) will remain within Password

Protected Partners Folders. All study personnel will have personal Login and Password Access, after undergoing the appropriate training in study protocols and documentation requirements.

Study data from data sheets will be regularly entered into the Research Electronic Data Capture (REDCap) system. This online data management system is secure and HIPAA compliant. The application is hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) and requires web authentication for access. Information in the system is transferred and saved using Secure Sockets Layer (SSL) encryption. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, develops this software application for electronic collection and management of research and clinical study data. The REDCap Consortium is composed of thousands of active institutional partners in over one hundred countries who utilize and support REDCap in various ways. As validated by Partners HealthCare, ERIS, and supported by Partners HealthCare Policies, REDCap has the controls necessary to collect data for 21 CFR Part 11 compliant studies. Our study will be supported by Partners ERIS EDC which will supply the required software validation and documentation necessary for different stages of the project.

Quality assurance is provided as part of the REDCap system. All changes to forms are automatically stored within a systems log. Additional validation of data entry will be performed by study staff on a regular basis to monitor for significant outliers and inconsistencies in data. All paper records including informed consent forms will be stored within locked cabinets in the cardiac surgery office. Office access is badge controlled.

XI) BIOSTATISTICAL ANALYSIS PLAN

STUDY VARIABLES

Eligibility Data

At onset of atrial fibrillation

Potential study participants who develop new onset atrial fibrillation following their cardiac surgery operations will be approached by study staff. The study will be explained, and these potential participants will be provided with study fliers and consent forms. Consent will not be obtained at this time. This will ensure that potential participants have adequate time to review the paperwork and consider enrollment in the intervention phase. At this time, study criteria will be reviewed by study staff and documented accordingly. Eligibility forms will be reviewed with the Principal Investigator. Potential participants who meet study criteria will be assigned a unique identifier at this time.

Demographics

At onset of atrial fibrillation

Demographic data assessed at the initial screening visit and recorded at the time of randomization will include date of birth, gender, ethnicity and primary language.

Comorbidities / Past Medical History

At onset of atrial fibrillation

Past medical history will be assessed at the time of screening and documented at the time of randomization. Data collected will relate to underlying cardiovascular pathology and to associated pathology of the pulmonary, renal, hepatic, endocrine, hematologic or neurologic systems.

Medications
At onset of atrial fibrillation; at time of discharge
Data on active medications will be collected at the time of initial screening, at randomization and at the time of discharge. This will include data on cardiac medications, antiplatelet therapy and major pulmonary therapies.

Operation Room History
At onset of atrial fibrillation
This form will collect data on operative details including date of the operation, time of departure from the operating room and procedures performed.

Perioperative Events
At onset of atrial fibrillation
Data on major post-operative complications and interventions will be assessed at the screening visit. This will include events like cerebrovascular accident, re-intubation or delayed extubation, acute kidney injury (AKI) and use of mechanical support (IABP, ECMO, etc.).

Informed Consent
At time of randomization (When diagnosed with recurrent or persistent atrial fibrillation)
Potential study participants who develop recurrent or persistent atrial fibrillation and meet study criteria will be approached to discuss randomization and enrollment in the intervention portion of the study. A complete explanation of the benefits and risks of the study will be provided, and patients will be given the opportunity to ask questions about all aspects of the study. The informed consent process will be documented for each potential subject who meets randomization criteria.

Heart Rate, EKG and Telemetry Assessment
At time of randomization; during inpatient follow-up and at discharge; at clinic visits; at study exit
Heart Rate, EKG and telemetry results will be collected at several points during the study via 12-leak EKG or inpatient telemetry monitors as appropriate. These data will be collected only after informed consent has been obtained.

Laboratory data
At time of randomization; during inpatient follow-up and at discharge; at outpatient INR checks
Laboratory data including but not limited to CBC, CMP, LFTS and INR will be collected at different points during the study. These data will only be collected after informed consent has been obtained.

Data on Rate and Rhythm Interventions
At time of randomization; during inpatient follow-up and at discharge; at clinic visits; at study exit
Data on rate and rhythm control medications and procedures used to manage atrial fibrillation will be collected at different points during the study. These data will only be collected after informed consent has been obtained.

Inpatient Events / Procedures
During inpatient follow-up and at discharge

Data on events and procedures that occur while patients are admitted will be collected on an ongoing basis while study participants are admitted to the hospital. Where complications occur, adverse event forms will be completed as well and principal investigators will be notified.

Secondary Outcomes
During inpatient and outpatient follow up; at discharge; at clinic visits; at study exit
Data on all secondary outcomes (as previously defined) will be collected and updated throughout the course of the study

Length of Stay Data
At discharge; at study exit
Data on length of stay will be collected at the time of discharge from the hospital and at study exit. This will include data on duration of any readmission episodes. At study exit, length of stay will be adjusted to account for readmission to the hospital

Rehabilitation and Recovery Data
At discharge; during outpatient follow up including phone; at study exit
Data on progress with postoperative recovery and rehabilitation will be collected at every post-discharge interaction including those by phone and in person. This will include questions about ongoing physical or other therapy, about readmissions, and about any post-discharge procedures.

Adverse Events and Interventions
During inpatient and outpatient follow up; At study exit
An adverse event form will be completed for all adverse events – including mortality – that occur for enrolled study participants. Recording will occur on an ongoing basis and the PIs will be notified of these events. Data collected in relation to adverse events will include onset, duration, grade (severity), relationship to study drugs and required interventions. Determinations of severity of events and association with study interventions will be made by PIs and will guide decision making about reporting

Atrial Fibrillation Quality of Life Data
During outpatient follow up (Surgery clinic and/or phone)
A quality of life questionnaire will be administered in person at the cardiac surgery clinic visit or over the phone at the 2-week phone call. This will incorporate several atrial fibrillation specific factors that affect patient quality of life.

Anticoagulation Cost Data
During outpatient follow up; at study exit
Financial data related to anticoagulation including cost of the medications and cost of transportation for outpatient INR monitoring (based on mileage) will be collected during outpatient visits and at the exit interview.

Final Anticoagulation Plan
During outpatient follow up; at study exit
At the four-week cardiology clinic visit and/or at the exit interview at 6 weeks, this form will be completed to document the final plan for anticoagulation after study completion. Decisions about therapy (need to continue and drug of choice) will be made by the cardiologist in conjunction with the patient. In the event that ongoing therapeutic anticoagulation is required for persistent atrial fibrillation, and the decision is made by the patient and cardiologist to switch therapies, the transition to an anticoagulation monitoring

service (if needed) will be facilitated by study staff and clinical providers from cardiology and cardiac surgery. INR levels will be followed by the patient's primary care doctor, patient's cardiologist or the anticoagulation management service depending on their cardiologist's preferences.

RANDOMIZATION

Patients who meet criteria for the intervention arm of the study will be randomized 1:1 to anticoagulation prophylaxis using warfarin or rivaroxaban. Randomization will be performed using a block design with block size of 6 participants. Randomization will be stratified by cardiac surgery operation performed.

The sequence of randomization will be predetermined using random number generation from statistical analysis software. Allocation will thus be pre-determined (prior to study initiation) as it relates to sequence of participant entry into the study. Randomization will be performed by study staff with oversight from principal investigators.

STATISTICAL METHODS

Comparative Characteristics of Intervention Groups

The efficacy of randomization will be assessed by estimating the balance in characteristics across interventions arms. Assessments of balance will be made at multiple stages over the course of the trial including at the time of interim analysis, and at the final analysis. Categorical variables will be compared using Chi-Squared tests while continuous variables will be compared using the Student's T-test. Any significant imbalances will be appropriately adjusted for in outcomes analyses.

Analysis of Primary Efficacy Outcome

Length of stay will be used as the primary efficacy outcome for this trial. The primary analysis will be performed in intention-to-treat fashion using the T-test (Two-sided, 0.05 level) to compare the observed mean length of stay between the two groups. The null hypothesis will postulate that there is no significant difference in the length of stay (in days) for patients randomized to warfarin vs. those randomized to Rivaroxaban. Analysis assumptions will include independence of study groups and lognormal (or normal) distribution of data in each group.

Additional as-treated analyses will be performed to estimate the effect of cross-over in the study. Adjusted length of stay will also be compared between groups, factoring in emergency department presentations and re-hospitalizations following the index postoperative admission.

Analysis of Primary Safety Outcome

Rates of major bleeding as previously defined will be compared between study groups. Differences will be calculated (including estimation of relative risk) and significance assessed using Cox proportional hazards modeling (One sided, 0.05 significance level). For these models, treatment group will be applied as an independent variable while major bleeding will be applied as the outcome.

Analysis of Secondary Outcomes

Cox proportional hazard models with parameters as specified above will be used to compared rates of occurrence of secondary outcomes between intervention arms. Event rates and relative risks will also be

estimated for each of these outcomes. Analyses will be performed based on both intention-to-treat and as-treated classifications. The following secondary outcomes will be analyzed:

- Cerebrovascular accident (Including stroke and TIA)
- Systemic arterial thrombo-embolism
- Minor bleeding
- Hospital readmission
- Cardiac rhythm at study conclusion
- All cause death
- Pericardial effusion
- Venous thromboembolism
- Acute kidney injury
- Infection
- Heart failure
- Myocardial infarction
- Hepatic dysfunction

Additional analyses will compare average costs of anticoagulation therapy (including monitoring costs) and average scores on quality of life tests using T-tests with parameters that mirror those used in the primary analysis.

POWER ANALYSIS

Sample size calculations are estimated based on existing retrospective data comparing length of stay for patients with postoperative atrial fibrillation managed with warfarin vs. rivaroxaban. Using these data, the study was designed to generate adequate power to detect meaningful differences in length of stay between the two study arms.

Based on prior retrospective analysis, the average length of stay for patients managed with Warfarin is estimated as 7.5 days compared with 6.5 days for patients managed with Rivaroxaban [Anderson E, Johnke K, Leedahl D, et al. Novel oral anticoagulants vs warfarin for the management of postoperative atrial fibrillation: clinical outcomes and cost analysis. Am J Surg. 2015 Dec; 210 (6):1095-102; PubMed PMID: 26482512.]. For our study, we estimate a 2-day difference and an anticipated standard deviation of 6 days in each group. 80% power will be generated with 2-sided confidence interval of 0.05 from a sample size of 266 patients (133 per group). Estimating 10-15% attrition and/or cross-over, over the course of the study, investigators originally aimed to enroll ~300 patients for study completion. This power estimation assumes a lognormal distribution of the data. With the modified enrollment target of 100 patients, the power estimation is ~65%.

XII) RISKS AND DISCOMFORTS

DRUG TOXICITIES

Study medications will be associated with some toxicity. Major potential toxicities as described on drug package inserts are summarized below. For study purposes, toxicity will be graded as follows:

- **Grade 1 (Mild):** Occurrence of an event that is well tolerated by the patient and managed without procedural intervention

- **Grade 2 (Moderate):** Occurrence of an event that causes interference with normal recovery and activity. May require pharmacological treatment and minor procedural intervention, but effects are not expected to be lasting.

- **Grade 3 (Severe):** Occurrence of an event that causes debilitation and significantly slows down recovery. Effects are expected to be lasting. May require pharmacologic treatment and/or major procedural intervention.

Wherever suspected, PIs will assess the clinical scenario surrounding adverse events to assess the likelihood that occurrence is directly related to the administration of study drugs. Monitoring at regular intervals (at the time of suspected toxicity and every two weeks) will guide decision making about changes in protocol and about need for termination of the study.

Warfarin Toxicities

Potential toxicities associated with Warfarin use include (See associated drug packaging insert):

- **Hemorrhage:** Including major and fatal bleeding. Bleeding occurs most commonly within the first month on therapy and most commonly in the setting of INR levels > 4.0. Certain patients are at increased risk including those with history of CVA or GI bleeding, older patients (Age > 65), those with history of malignancy, trauma, renal or hepatic impairment, certain genetic predispositions and history of variable INRS with anticoagulation treatment. Bleeding risk is mitigated by regular INR monitoring in all patients with increased monitoring frequency for high risk patients, in the setting of dose changes or for patients on drugs that may interact with warfarin. Warfarin should be discontinued immediately if there is any concern for bleeding and reversed as needed (See section on reversal of anticoagulant effect).

- **Necrosis of skin and other tissues:** Necrosis and gangrene occur rarely with warfarin use but may have serious manifestations. These toxicities typically occur early on after initiation of warfarin therapy and in the most serious situations require tissue debridement and/or amputation. Warfarin should be discontinued immediately if there is any suspicion for necrosis. Warfarin should be avoided in patients with a recent history of heparin induced thrombocytopenia as it has been associated with subsequent limb ischemia, necrosis and death. Warfarin may be used after complete recovery and stabilization of platelet counts.

- **Systemic and cholesterol embolization**: Warfarin therapy may increase the risk of release of atheromatous plaque emboli with varying presentations depending on the site of systemic

embolization. Symptoms can range from pain and organ dysfunction from visceral hypoperfusion, to tissue necrosis particularly in extremities. Warfarin therapy should be discontinued if any suspicion for therapy related embolization.

- **Pregnancy related disorders:** Including fetal death, pregnancy loss and fetal birth defects. Warfarin is contraindicated in pregnancy. Pregnant patients will be excluded from this study and adequate birth control practices will be ensured for study participants

- **Immune disorders:** This includes allergic reactions and anaphylaxis

- **Vascular disorders:** Including vasculitis

- **Hepatobiliary disorders**: Including elevation of liver enzymes and hepatitis

- **Gastrointestinal disorders**: Including nausea, vomiting, diarrhea, abdominal pain, bloating, flatulence dysgeusia

- **Skin disorders:** Including rash, pruritis, dermatitis, alopecia

- **Respiratory disorders:** Including tracheobronchial calcification

Rivaroxaban Toxicities

Potential toxicities associated with Rivaroxaban use include (See associated drug packaging insert):

- **Hemorrhage:** Including major and fatal bleeding. Certain patients are at increased risk including those with history of CVA or GI bleeding, older patients (Age > 65), those with history of malignancy, trauma, renal or hepatic impairment and certain genetic predispositions. Bleeding risk is mitigated by close clinical and CBC monitoring in high risk patients, in the setting of dose changes or for patients on drugs that may interact with Rivaroxaban. Rivaroxaban therapy should be discontinued immediately if there is any concern for bleeding and reversed as needed (See section on reversal of anticoagulant effect).

- **Increased CVA Risk after discontinuation:** Stopping Rivaroxaban in the absence of adequate anticoagulation for underlying pathology increases the risk of thrombotic events. If Rivaroxaban treatment is discontinued for any reason other than completion of therapy or bleeding event, coverage with an alternative agent should be considered

- **Spinal/epidural hematoma:** Risk of spinal hematoma is significant in patients on Rivaroxaban who receive neuraxial anesthesia or spinal puncture. Placement or removal of catheter, and performance of procedures should only take placed when anticoagulant effect of Rivaroxaban is low (No sooner than 18 hours after last administration of Rivaroxaban). Following procedures, resumption of Rivaroxaban may be delayed based on concern for bleeding.

- **Gastrointestinal disorders:** Including oropharyngeal pain, abdominal pain, dyspepsia, toothache

- **Constitutional disorders:** Including fatigue

- **Infectious disorders:** Including sinusitis and urinary tract infection
- **Musculoskeletal and connective tissue disorders:** Including osteoarthritis and back pain
- **Nervous system disorders:** Including syncope
- **Skin and subcutaneous tissue disorders**: Including pruritus and blisters

PSYCHOSOCIAL RISK

Psychosocial risks associated with study participation will include the potential for psychological stress from being involved in an investigational study and having to interact with study staff, as well as the inconvenience of having to interact with study staff at regular intervals, including travel to study visits where necessary. Participants may also be concerned about the effects of study enrollment (or later withdrawal from the study) on interactions with providers. Additional risks relate to concerns about data safety and confidentiality of data collected during the study.

Study approach to mitigation of psychosocial risks will be multifaceted and will include:

- Emphasis on provision of detailed study information at the time of registration to ensure that potential participants are fully aware of the study procedures and risks
- Reassurance provided to study participants about monitoring protocols and safe guards provided in the study
- Explanation of potential personal and society benefits of participation to study participants
- Limitation of direct interaction with participants to pre-specified visits as outlined in the study procedures, and additional necessary communications as dictated by the clinical situations
- Reassurance provided to study participants that involvement in study or future decision to withdraw will have no implications for relationship with primary providers
- Maintenance of careful data protection strategies as outlined earlier in the proposal

XIII) POTENTIAL BENEFITS

POTENTIAL BENEFTIS TO PARTICIPATING INDIVIDUALS

Individual study participants randomized to the Rivaroxaban group may benefit from decreased hospital length of stay following cardiac operations with associated decreases in hospital costs. Additional potential benefits following discharge will include decrease in social disruptions from having to undergo routine testing at least weekly in the outpatient setting, with meaningful implications for travel, work and overall societal productivity. Furthermore, repetitive and occasionally stringent dietary routines are required to maintain INR in the therapeutic range while on warfarin therapy. Patients on Rivaroxaban will not have these restrictions. Study participants will thus have the potential to benefit from more freedom and variety in meal planning.

POTENTIAL BENEFITS TO SOCIETY

Should study results demonstrate efficacy and safety or Rivaroxaban in the defined population, future cardiac surgery patients will enjoy the same benefits outlined above. On a societal level, decreased costs may contribute to more optimal utilization of healthcare funds. More globally, study findings will provide backing to explore Rivaroxaban and other novel oral anticoagulants for indications beyond non-valvular atrial fibrillation including arterial thromboembolism prophylaxis in patients with mitral stenosis and/or mechanical prosthetic valves. Many patients are on life-long therapeutic anticoagulation with potential for significant social and financial benefit if novel oral anticoagulants are found to be effective for the specific indications.

XIV) MONITORING AND QUALITY ASSURANCE

Study monitoring and safety assessment will be performed by an internal study monitoring committee made up of study PIs and select study staff. The committee will aim to perform functions that address the ethical issues that affect study participations. This committee will convene every two weeks and evaluate several aspects of the study as outlined below:

MONITORING OF SOURCE DATA

Monitoring of data collection validity and integrity, and adherence to the IRB approve study protocol will be performed on a regular basis by study staff and study PIs. This will include review of accuracy and completeness of case entry records with special consideration of outliers and thematic data patterns. Data management will be performed with the REDCap online system which will log all entries and monitor changes in data fields through a careful data audit process. Patterns in collected data will be discussed at fortnightly internal monitoring committee meetings. An interim analysis will be performed midway during the study after 30 patients have been enrolled in each intervention arm.

SAFETY MONITORING

Principal investigators will be made aware of adverse events by inpatient teams and study staff at the time of occurrence. Rates and patterns of occurrence of adverse events (including primary safety outcomes) will be monitored on an ongoing basis by PIs, with formal review at internal monitoring committee meetings every two weeks. This review will include chart review for all enrolled participants and discussion about phone calls with discharged study participants to capture outpatient events.

OUTCOMES MONITORING

Rates of study outcomes including adverse events will be monitored on an ongoing basis by study staff and study PIs. Scheduled twice-monthly internal monitoring committee meetings will explore the rates of occurrences of primary efficacy and safety outcomes with accompanying conversations about the overall trajectory of the study. Following enrollment of at least 20 patients in each group, any indication that outcomes are skewed in favor of one group or the other will be carefully explored and discussed with the IRB. This information will guide decisions about study discontinuation, if appropriate.

REPORTING OF ADVERSE EVENTS

All grade 3 adverse events will be reported immediately to the IRB. Adverse events of grade 2 or lower severity that occur more frequently than reported in the existing literature will also be reported to the IRB (Rates will be estimated and maintained following the enrollment of 20 or more patients in each study arm). Reportable events will include adverse events as defined above under “secondary outcomes”, pregnancy, laboratory abnormalities and any concerns for drug overdose.

Suspected adverse events will also be reported to the FDA according to requirements specified through clinical trials.gov.

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XVI) APPENDIX

LIST OF ACCOMPANYING DOCUMENTS

- Study schema
- Study Informed Consent Form
- Warfarin drug package inserts
- Rivaroxaban drug package inserts