Academic and Community Cancer Research United (ACCRU)

A Phase III, Randomized, Controlled, Double-Blind Study Evaluating the Safety of Two Doses of Apixaban for Secondary Prevention of Cancer Related Venous Thrombosis in Subjects Who Have Completed at Least Six Months of Anticoagulation Therapy

For any communications regarding this protocol, please contact the protocol resource person on the following page.

Study Chairs

ACCRU: [redacted]

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Drug Availability

Drug Company Supplied: Apixaban (Eliquis®) – IND #134645

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center

[redacted]

Document History	**Effective Date**
Pre-activation ACCRU	December 23, 2016
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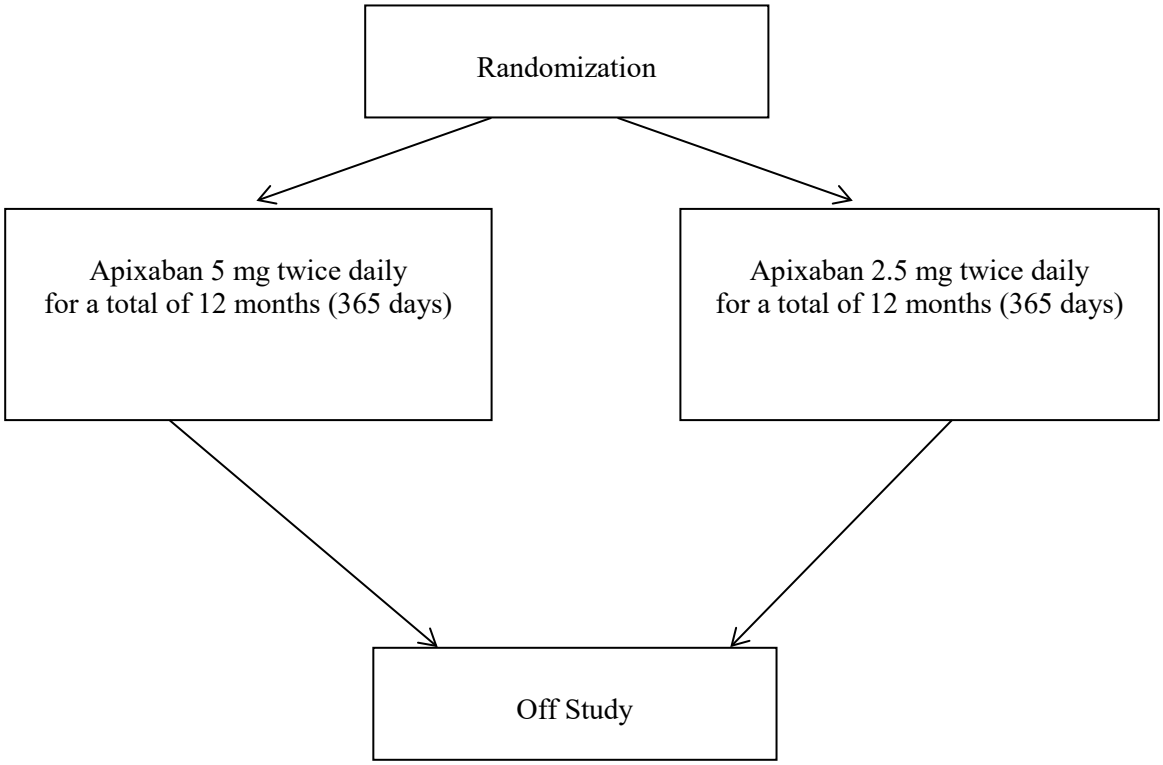
Index

Schema



Unacceptable adverse events or patient refusal at any time → Off Study

1 Cycle = 30 days

Generic name: Apixaban
Brand name(s): Eliquis®
Availability: Biologics, Inc.

1.0 Background

1.1 Treatment

Active cancer is associated with a markedly increased risk of both incident and recurrent venous thromboembolism. The rate of recurrence has been estimated to be between 2 to 9 fold higher compared to patients without cancer (1-8). For those cancer patients who suffer a VTE recurrence, the risk of death is increased 3-fold particularly if the recurrent event is a pulmonary embolism (9). In keeping with these data, current guidelines recommend continued anticoagulation therapy beyond the acute treatment phase of 3 – 6 months until there is no longer evidence of active cancer (10). This recommendation distinguishes primary treatment (first 3 – 6 months following VTE confirmation) from secondary prevention which includes continued treatment beyond 6 months. These guideline recommendations however are based on scant data with an evidence grade limited to expert opinion only (Grade 2C)(10). Of note, patients with cancer also carry an increased risk of anticoagulant associated major bleeding (2, 5, 11-14). Balancing the risk of VTE recurrence with the risk of anticoagulant associated major bleeding complicates decision making for these patients. Prolonged anticoagulant therapy may not be beneficial for all cancer patients and may indeed provoke harm in some. In the end, there are limited data to inform decision making for these patients beyond 6 months of therapy.

The LITE investigators randomized 200 cancer patients to receive warfarin or low molecular weight heparin (tinzaparin) for 3 months for the acute treatment of VTE (15). Thereafter, patients were assessed for an additional 9 months following anticoagulation discontinuation. At three months, 6% of those patients randomized to tinzaparin compared to 10% on warfarin suffered an acute VTE recurrence which did not differ significantly between treatment allocations. At 12 months, an additional 7% of patients in the tinzaparin group (total of 13%) compared to an additional 16% in the warfarin arm (total of 26%) suffered VTE recurrence (p=0.044; risk ratio 0.44; absolute difference 9.0%, (95% CI -21.7% to -0.7%)). Major bleeding events were 7% for both groups at 3 months. Death occurred in 20% for both groups at 3 months and 47% of both groups at 12 months. The high rate of VTE recurrence and death can be appreciated following anticoagulation discontinuation.

The DACUS trial assessed cancer patients with first episode of DVT who had been treated with low molecular weight heparin (LMWH) for 6 months (16). After 6 months, patients underwent duplex ultrasound imaging to assess residual DVT. Those with residual thrombus were then randomly assigned to continue LMWH for an additional 6 months or to discontinue therapy. For those patients with thrombus resolution (no residual thrombus), anticoagulation was discontinued. They enrolled 347 patients of whom 242 patients had residual DVT. Of these, recurrence occurred in 22 of the 119 patients (18%) with continued LMWH compared to 27 of 123 patients (22%) who stopped therapy. For those patients without residual thrombus, the recurrence rate was low at 2.9% (3/105 patients). This study suggests that continued anticoagulant therapy beyond 6 months based on ultrasound evidence of residual thrombus provides only a modest reduction in recurrent venous thromboembolism. As such, this study does not support current guidelines for extending secondary prevention with prolonged LMWH therapy beyond 6 months. Furthermore, decisions based on the presence of residual thrombus after acute therapy has not been deemed sufficiently well validated to receive guideline endorsement. Moreover, this information is not sufficient to meet clinical

equipoise when considering a randomized trial design in cancer patients. For patients with active cancer who have completed 6 month of anticoagulants, there would be little appetite for a randomized trial where one group might be randomized to placebo given the high rate of VTE recurrence in these patients.

Guideline recommendations for patients with VTE in the setting of an active malignancy include extended anticoagulation with LMWH as the preferred anticoagulant regardless of the bleeding risk (10). Anticoagulants are often continued until there is no evidence of active malignancy defined as any evidence of cancer on cross-sectional imaging or any cancer related treatment (surgery, radiation, or chemotherapy) within the past 6 months. Chronic LMWH therapy however has several disadvantages. First, LMWH is given by subcutaneous injections which may be painful and cause considerable local ecchymoses and hematomas. Second, the cost of LMWH may be prohibitive. For individuals without insurance, this can be more than $100 USD daily. Because this treatment is often given for months on end, health-care costs for medications alone can be thousands of dollars. Third, thrombocytopenia associated with the cancer or cancer treatments limit its use and raise clinical concerns regarding possible heparin induced thrombocytopenia. Fourth, there is neither a specific nor effective proven antidote should the patient develop bleeding complications. Fifth, renal failure which can be common with cancer or cancer related treatment limits the use of this medication. For these combined reasons, an alternative anticoagulation therapy for patients with cancer associated VTE would be extremely attractive.

1.2 Investigational Agent

Apixaban (Eliquis) is an oral direct factor Xa inhibitor which impairs coagulation by inhibiting the conversion of prothrombin to thrombin. It does not require antithrombin for antithrombotic activity and inhibits both free and clot-bound FXa. Apixaban has a half-life of about 12 hours and thus is dosed twice-daily. Bioavailability is approximately 50% after oral dosing with maximum concentrations at 4 hours post ingestion. The pharmacokinetics are linear and plasma protein binding in humans is high at approximately 87% with a volume of distribution of approximately 21 liters. Apixaban is metabolized in the liver mainly via the CYP3A4 pathway. Renal excretion accounts for about 27% of total clearance. Approximately 25% of the drug is eliminated in the feces. This drug is not dialyzable due to its high plasma protein binding. (“The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.”) Apixaban is currently FDA approved for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy, for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery and reducing the risk of stroke/systemic embolism in the setting of non-valvular atrial fibrillation.

1.3 Clinical Data to Date

The AMPLIFY investigators randomized 5395 patients with acute VTE to either apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) or enoxaparin/warfarin (17). The primary efficacy outcome, recurrent symptomatic VTE or death related to VTE, occurred in 2.3% in the apixaban group compared to 2.7% in the conventional-therapy group. From an efficacy standpoint, apixaban was therefore deemed non-inferior to standard anticoagulant therapy. Both major bleeding and the

composite of major plus non-major yet clinically relevant bleeding were significantly lower for patients receiving apixaban. The AMPLIFY-EXT investigators randomized 2482 patients with VTE who had recently completed 6 – 12 months of anticoagulation to receive one of two doses of apixaban (5 mg twice daily or 2.5 mg twice daily) or placebo for an additional 12 months. Both apixaban doses reduced recurrent VTE without increasing major bleeding compared to placebo (18).

There are now 10 studies comparing direct oral factor inhibitors with conventional anticoagulation for treatment of patients with VTE (19). A recent metaanalysis was performed to assess the safety and efficacy of direct factor inhibitors in cancer patients with VTE by combining all of the cancer patients from each study. Patients from 6 of the 10 studies were included (dabigatran 2 studies, rivaroxaban 2 studies, edoxaban 1 study, and apixaban 1 study). Combined there were 1,132 cancer patients evaluated. Based on each of the studies included, the comparator was conventional anticoagulation with heparin and warfarin. Venous thromboembolism occurred in 3.9% of patients treated with a direct factor inhibitor and 6.0% in those assigned to conventional therapy. These rates did not differ statistically. Major bleeding occurred in 3.2% of patients treated with a direct factor inhibitor and 4.2% in those assigned to conventional therapy which also did not differ. Based on these data, direct factor inhibitor therapy appears both effective and safe compared to conventional therapy in cancer patients.

Despite these trial results, apixaban is not currently recommended for cancer related VTE treatment or secondary prevention for several reasons. First, there are limited data supporting the use of apixaban in cancer patients with no trials specifically designed to evaluate its utility in cancer patients. In the AMPLIFY treatment trial, only 2.65% (143 patients) had underlying cancer as a risk factor with only 66 patients with active cancer in the apixaban arm. In the AMPLIFY Extend trial, only 42 patients with active cancer were enrolled. Indeed, the latest guideline regarding cancer associated VTE (10) recommended against the use of apixaban (or other direct oral factor inhibitors). These recommendations however were given a very weak strength (Grade 2C) given the lack of supporting data.

In the AMPLIFY Extend trial, the comparator was placebo. This would not likely be embraced or even ethical in cancer patients with a VTE history for several reasons. First, opinion leaders in the field often recommend against the use of factor Xa inhibitors in cancer patients with VTE (personal communication). Second, many of our patients are concerned about starting a novel anticoagulant for cancer associated VTE treatment in the absence of data (personal experience). Irrespective of this knowledge limitation, the hypothesis supporting the use of apixaban in cancer related VTE management remains quite attractive. A current ACCRU trial is investigating the worth of apixaban vs LMWH for the treatment of clots in cancer patients, for 6 months.

In order to gain guideline endorsement for prolonged secondary prevention, apixaban must be assessed in a randomized controlled trial setting. The current standard of care for these patients is continued LMWH for cancer associated VTE. The guidelines favor extended anticoagulant therapy with no scheduled stop date over shorter predetermined durations irrespective of the bleeding risk.

1.4 Dose Rationale and Risk/Benefits for an Extended Period in Cancer Patients

The AMPLIFY-EXT investigators compared apixaban 5 mg twice daily or 2.5 mg twice daily to placebo in 2486 patients who had completed 6 to 12 months of anticoagulant therapy for whom there was clinical equipoise regarding continuation or cessation of anticoagulant therapy (18). The vast majority of these patients had no history of active cancer. At 12 months of follow up, recurrent VTE occurred in 1.7% of patients randomized to apixaban 2.5 mg and 1.7% for those patients randomized to apixaban 5 mg twice daily. This compared to 8.8% in the placebo arm meeting the criteria for superiority for both doses. The use of apixaban 2.5 mg was associated with a 7.2% absolute reduction of VTE recurrence (95% CI, 5.0 to 9.3; P<0.001). The 5 mg dose was associated with a 7% absolute risk reduction (95% CI, 4.9 to 9.1; P<0.001). Major bleeding was infrequent and did not differ between treatment groups: apixaban 2.5 mg (0.2%), 5 mg (0.1%) and placebo groups (0.5%). Clinically relevant non-major bleeding likewise did not differ between groups: 2.3% (placebo), 3.0% (apixaban 2.5 mg) and 4.2% (apixaban 5 mg). Based on these data, both apixaban 2.5 mg or 5 mg twice daily are attractive for extended "secondary prevention" for patients without cancer associated VTE. We hypothesize that apixaban will provide safe and effective secondary prevention for patients with cancer associated VTE who have completed 6 months (but no more than 12 months) of anticoagulant therapy.

1.5 General Design

This is a multicenter, randomized, double blind, superiority trial for safety. Participating centers will be from the Academic and Community Cancer Research United (ACCRU) research consortium. This research consortium is comprised of more than 80 leading academic institutions and community oncology practices in the United States and Canada. The goal of this consortium is to collaborate with industry partners to develop and conduct clinical trials in cancer research.

Subjects will be screened at both outpatient clinic visit appointments and during hospitalizations using direct referrals or by daily automated screening of the electronic medical record. Interested qualified subjects will be consented and offered participation in this trial. Subjects will be considered for trial participation if they have evidence of active cancer and have a history of a documented venous thrombotic event for which they have received at least 6 months (but not more than 12 months) of anticoagulant therapy. Both the date and location of the original thrombosis will be recorded, as well as the anticoagulant used for the original treatment. After randomization, patients will be allocated to receive either apixaban 5 mg twice daily or 2.5 mg twice daily. Allocation to treatment will be done centrally. Once consent has been obtained, baseline laboratory values will be established and subjects will begin treatment and follow-up for 12 months.

The principal safety outcome will be a combined endpoint of major bleeding plus clinically relevant non-major bleeding. All episodes of major bleeding, clinically relevant non-major bleeding and deaths will be evaluated by a central, blinded, independent adjudication committee. Adjudication results will be the basis for the final analyses. An independent data and safety monitoring board (DSMB) will monitor the patients' safety and give recommendations to the executive committee.

2.0 Goals

2.1 Primary Safety Endpoint

2.11 The primary safety endpoint will include the combined endpoint: any episode of major bleeding including fatal bleeding or clinically relevant non major bleeding. In particular, we will consider the proportion of patients who experience at least one such bleeding event within 12 months of beginning treatment. The following criteria will be used to confirm and categorize a bleeding episode:

- Major bleeding is defined as overt bleeding plus a hemoglobin decrease of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red blood cells, or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intra-articular, intramuscular with compartment syndrome or fatal bleeding. Intracranial hemorrhage includes intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds (21).

- Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with a member of the health care team, or temporary cessation of study treatment.

- Minor bleeding is defined as overt bleeding that did not meet criteria for major bleeding or clinically relevant non-major bleeding.

2.2 Secondary Safety Endpoint

2.21 The secondary safety endpoint will be the same as the primary safety endpoint, but in this case we will consider the proportion of patients who experienced at least one such bleeding event within 6 months of beginning treatment, as this was the primary endpoint in previous studies.

2.3 Secondary Efficacy Endpoint

2.31 The secondary efficacy endpoint of this study will be VTE recurrence including DVT, PE, fatal PE, or arterial thromboembolism. The following criteria will be used to confirm and categorize a VTE recurrence:

- Suspected (recurrent) DVT: The original DVT must be confirmed by duplex ultrasonography, venography, CT, or MRI. A recurrent DVT must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

- Suspected (recurrent) PE: The original PE must be confirmed by CT, MR, conventional pulmonary angiography, or VQ perfusion imaging. A recurrent PE must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

- Fatal PE: PE based on objective diagnostic testing, autopsy, or death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death).

- Incidental VTE recurrence: Due to the nature of cancer surveillance related imaging, it is anticipated that recurrent venous thrombosis or thrombus propagation may be identified. In order to be classified as an event, the thrombus in question must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

- Arterial thromboembolism: Myocardial infarction (MI), stroke, transient ischemic attack (TIA), or peripheral arterial embolism.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Confirmed acute index (original venous thrombotic) event: lower extremity or upper extremity (jugular, innominate, subclavian, axillary, brachial) DVT, PE, splanchnic (hepatic, portal, splenic, mesenteric, renal, gonadal), or cerebral vein thrombosis for which the patient has received ≥180 days (but ≤365 days) of anticoagulant therapy prior to registration. The date, imaging modality, and location of index event will be required. The date of initiation and specific type of anticoagulants used will also be required.

3.13 Active cancer defined as metastatic disease and/or any evidence of cancer on cross-sectional or PET imaging, cancer related surgery, chemotherapy or radiation therapy within the past 6 months. Note: non-melanoma skin cancer does not meet the cancer requirement.

3.14 Life expectancy ≥ 6 months.

3.15 ECOG Performance Status (PS) of 0, 1, or 2. (Form is available on the ACCRU web site [redacted]

3.16 The following laboratory values obtained ≤30 days prior to registration.
- Hemoglobin ≥8 g/dL
- Platelet count ≥50,000/mm^3
- Alanine aminotransferase (ALT) or Aspartate transaminase (AST) ≤3 x ULN
- Calculated creatinine clearance must be ≥30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}} \text{ *(0.85)}$

3.17 Negative serum or urine pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.
Note: A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

3.18 Ability to provide informed written consent.

3.19 Willing to undergo monthly follow-up assessment, either in person at the enrolling institution or by telephone (script in Appendix V).

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception
    - Note: Women of child bearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 33 days after finishing the last dose.
    - Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 93 days after finishing the last dose.
    - Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Note: Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

3.22 Active major bleeding.

3.23 Severe hypersensitivity reaction to apixaban (e.g., anaphylactic reactions).

3.24 Current use of strong CYP3A4 inducers or inhibitors (see list in appendix II). NOTE: Patients may be eligible if they transition to an alternative agent (see section 8.1) or are able to stop CYP3A4 inducer or inhibitor.

3.25 Current use of thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) that will be continued on study.

3.26 Severe liver disease (known cirrhosis Childs Pugh class B or C), or active hepatitis.

3.27 Documented venous thromboembolism while on therapeutic anticoagulation ("anticoagulation failure").

3.28 Mechanical heart valve.

3.28 Documented hemorrhagic tendencies (e.g., hemophilia).

3.29 Bacterial endocarditis.

3.30 Any of the following conditions:
- Intracranial bleeding ≤6 months prior to randomization
- Intraocular bleeding ≤6 months prior to randomization
- Gastrointestinal bleeding and/or endoscopically proven ulcer ≤6 months prior to randomization
- Head trauma or major trauma ≤1 month prior to randomization
- Neurosurgery ≤2 weeks prior to randomization
- Major surgery ≤1 week prior to randomization
- Gross hematuria at the time of randomization

4.0 Test Schedule

Tests and procedures	≤30_days prior to registration (baseline)	Every 30 days after the start of treatment (± 1 week)[3]	End of treatment
History and exam (including height and weight)	X		
ECOG PS	X	X	
Adverse event assessment[3]	X	X	X
Hematology: • CBC	X[1]		
Chemistry: • SGOT (AST) or ALT • Creatinine	X[1]		
Selected concomitant meds[3] (see CRF for this form)	X	X	X
Pregnancy test[2]	X		
Patient education regarding signs and symptoms of thrombosis (Appendix VI)	X[5]		
Patient Contact (including bleeding assessment, see App. IV and V)[3]	X	X	X
Patient compliance documentation[4]		X	X

1. ≤30 days prior to registration.
2. For women of childbearing potential only. Negative serum or urine pregnancy test done ≤7 days prior to registration.
3. If it is not feasible for the patient to return to the enrolling center for the monthly reassessment, a detailed history will be obtained by phone using a structured interview (see appendix V).
4. Use the questions in Appendix VII to obtain this information, and document the information on the appropriate case report form.
5. Prior to 1st study drug administration: Appendix VI given to patient and patient educated on signs/symptoms of potential thrombosis to monitor and report to study staff.

5.0 Stratification Factors

5.1 Cancer stage: Residual (intact primary or metastatic) vs. no residual (no evidence of disease).

5.2 Risk: High risk vs. lower risk using validated Khorana score (see appendix III).

5.3 Location of initial thrombosis: deep-vein thrombosis (including atypical VTE) vs. pulmonary embolism.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the ACCRU web page at [redacted] click on "Training Page" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available by using the Help button. Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.13 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.14 Treatment cannot begin prior to registration and must begin ≤30 days after registration.

6.15 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.16 Treatment on this protocol must commence at an ACCRU institution under the supervision of a health care professional.

6.17 Study drug is available on site.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock-Simon).

- Apixaban 2.5 mg twice daily.
- Apixaban 5 mg twice daily.

6.3 Procedures for Double-Blinding the Treatment Assignment

6.31 After the treatment assignment has been ascertained by the registration/randomization application, the patient's study medication code number will be displayed on the confirmation of registration screen.

6.32 The data manager/nurse/pharmacist at the patient's institution must contact the ACCRU Registration Office for a code number when additional study product is needed for the patient.

6.33 ACCRU Registration Office personnel will monitor the supply of coded bottles at each participating institution and will arrange for the oncology pharmacist to send further supplies to the participating institutions as needed.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose Level	Frequency	Route
Apixaban	2.5 mg	Twice daily for 12 months (365 days)	Oral
Apixaban	5 mg	Twice for daily 12 months (365 days)	Oral

*If a dose of apixaban is not taken at the scheduled time, the dose should be taken as soon as possible (+/-4 hours of the normal scheduled dose) on the same day and the prescribed dosing schedule should be resumed. If more than 4 hours late, then just wait for the next dose. The dose should not be doubled to make up for missed doses.

7.11 Scheduled visits every 30 days +/- 1 week (either in person or by scripted telephone interview with a study coordinator) should include a standardized assessment for recurrent thromboembolism, bleeding episodes, and adverse reactions. Patients should be instructed to report to the clinic immediately (or call 911/go to the Emergency Room) if they had any bleeding, or symptoms of recurrent deep-vein thrombosis, pulmonary embolism, or both. Written patient education materials will be provided to each patient outlining signs and symptoms to watch for regarding VTE recurrences (appendix VI). All suspected episodes of recurrent thrombosis should be investigated with the use of objective imaging.

7.2 Post protocol completion: Anticoagulation decision algorithm

7.21 Following the 12 months of protocol completion, a decision regarding anticoagulation continuation (off-study) will be clinically determined by the medical team caring for the patient. Although cancer is associated with a high risk of recurrent venous thromboembolism, the rate of recurrence differs significantly by cancer type, stage of disease, and stage progression over time (20). For the following patient characteristics, we recommend continuing anticoagulation: patients with brain, lung, pancreatic, or ovarian cancer; myeloproliferative or myelodysplastic disorders; stage IV cancer; cancer stage progression; or leg paresis. Anticoagulation options could include: continue apixaban (or other oral novel direct factor inhibitors), LMW heparin (dalteparin or enoxaparin), or warfarin.

For patients not meeting these specific criteria or if their presenting thrombus was limited to the calf (distal to and not including the popliteal vein), it is reasonable to discontinue anticoagulation therapy.

7.3 Breaking Codes in Double-Blinded Studies

The treatment code cannot be broken except in the event of an emergency for an individual patient. In the event of an emergency, call the ACCRU Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m.

Central Time. Place a call to the ACCRU Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can return the call the next business day. If a patient has been removed from the study and the clinician believes it is important to know what dose the patient was on, they can be unblinded. Before unblinding, all protocol data should be collected.

8.0 Dosage Modification Based on Adverse Events

8.1 Apixaban is cleared through several mechanisms including renal clearance, hepatic metabolism, and fecal excretion. Severe thrombocytopenia, liver and renal failure may increase bleeding risk. Patients with calculated creatinine clearance ≤30 ml/min (using the Cockcroft-Gault formula) must hold treatment until renal function improves to creatinine clearance >30 ml/min. They may get alternative anticoagulation treatment during this time period until renal function improves per the attending physician judgment.

For patients receiving either a strong CYP3A4 inducer or a strong CYP3A4 inhibitor (Appendix II), the medication should be discontinued or an alternative agent within the specific class of drug should be sought in order to participate in this study. If no good alternative agent within that class can be identified and the drug is required, the ACCRU Data Manager should be notified and the subject removed from the trial and go to observation.

For thrombocytopenia (> 50,000/microliter), no dose adjustment is necessary. For thrombocytopenia (< 50,000/microliter), apixaban will be held until platelet count recovers. Once the platelet count improves (≥ 50,000/microliter), the apixaban dose should be restarted.

If patients meet criteria for a major bleed, they will have met a major safety endpoint and will be removed from the study. The patient will then be managed, off-study, as appropriate per the clinical situation and current guidelines.

If patients meet criteria for a recurrent venous thromboembolic event, they will have met a major secondary endpoint and will be removed from the study. The patient will then be managed, off-study, as appropriate per the clinical situation and current guidelines.

If the patient suffers a non-major clinically relevant bleeding event, they will have met a major safety endpoint. Medical management will be provided in accordance with the location and severity of the bleeding event. This may include temporary cessation of study medication. Once the bleeding event has been appropriately managed, they can restart study medication, if considered clinically appropriate by the attending physician, and can be followed appropriately per protocol. They do not need to be removed from the study for this event.

8.2 **Patients requiring any invasive procedure requiring temporary anticoagulant cessation will be managed as follows:**

(1) Date and type of procedure will be recorded on the CRF;

(2) Apixaban will be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding, with no drug given on the procedure date; For low bleeding risk procedures, apixaban will be discontinued at least 24 hours prior to the procedure.

(3) Post procedure, the patient should receive appropriate DVT prophylaxis per institutional guidelines. This could include prophylactic apixaban (open label dose of 2.5 mg twice daily) dosing for 48 hours; the first prophylactic dose will be given 24 hours after the procedure. Alternatively, low molecular weight heparin or unfractionated heparin would be reasonable.

(4) Study drug will be withheld until 48 hours after the procedure and not initiated until adequate hemostasis is confirmed.

If apixaban treatment is temporarily held for any situation, the reason will be recorded on the CRF and the patient can go back on study for up to day 365 of the treatment schedule.

9.0 Ancillary Treatment/Supportive Care

9.1 Concomitant use of strong CYP3A4 inhibitors or inducers (appendix II) is prohibited.

9.2 Non-steroid anti-inflammatory drugs (NSAIDs) and antiplatelet agents (aspirin) are discouraged but not prohibited. If aspirin use is required, then the dose should be ≤100 mg daily. The use of these drugs should be recorded on the CRF.

9.3 **Note:** Antiplatelet therapy with a thienopyridine (clopidogrel, prasugrel, or ticagrelor) is an exclusion criterion and not allowed while on protocol therapy.

9.4 Measures necessary for minor and major bleeds should be utilized.

9.5 Other anticoagulants should not be used concomitantly (aside from those noted in Section 8.2).

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
[redacted]

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a Med Watch 3500A report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4 All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
    - Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol (determined based on Reference Safety Information from the current investigator brochure for Apixaban).

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 Special Situations for Expedited Reporting

10.311 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.312 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.313 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

    - Myelodysplastic syndrome (MDS)

    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.314 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.315 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The site investigator must immediately notify ACCRU of this event via the Pregnancy Surveillance Form (found in the forms packet) within 24 hours and in accordance with SAE reporting procedures in Section 10.4.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy

(eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

10.316 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

10.317 Adverse Events of Special Interest

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected:

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis. (NOTE: If liver toxicity becomes clinically apparent, it must be evaluated and then reported.)

Adverse drug reactions (related SAEs) should be reported. If hepatic failure, clearly occur due to the meta or primary malignancy, it should not be considered related, therefore not reportable to BMS.

10.318 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious adverse event, as appropriate, and reported accordingly.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to ACCRU **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to ACCRU within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">1 Business Day</td><td rowspan="2">24-hour 1 Business Day</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>1 Business Day</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 1 Business Day" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 1 business day of the initial 24-hour report.
- "1 Business Day" - A complete expedited report on the AE must be submitted within 1 business day of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 1 business day for:

- All Grade 4, and Grade 5 AEs

Expedited 1 business day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

2. Follow site-specific reporting guidelines.

3. Submit form 3500A to the FDA, MedWatch, [redacted]

4. Submit copies to the ACCRU SAE Coordinator via fax [redacted] The ACCRU SAE Coordinator will forward the report to Bristol-Myers Squibb via E-mail within 1 business day to [redacted]

   If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

   All SAEs should be followed to resolution or stabilization.

5. The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 All adverse events should be graded at each evaluation per the CTCAE v4.0 grading.

10.52 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also

be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.54 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Non-serious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Non-serious Adverse Events will be provided to BMS via the reconciliation report as outlined below.

10.55 Reconciliation

The Research Coordinating Center will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Reconciliation will occur every three months and once just prior to database lock/Final Study Report (FSR). BMS GPV&E will e-mail upon request from the Research Coordinating Center, the GPV&E reconciliation report. The data elements listed on the GPV&E safety data reconciliation report will be used for case identification purposes. If the Research Coordinating Center determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

11.0 Treatment Evaluation Using RECIST Guideline – Not applicable

12.0 Descriptive Factors – Not applicable

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go off study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted.
- If the patient never received treatment, on-study material must be submitted.

13.2 It is deemed a *major violation*, if protocol requirements regarding treatment of the patient in cycle 1 of the initial therapy are severely violated that evaluability for primary end

point is questionable. This determination needs to be made by an investigator blinded to treatment allocation.

13.3 It is deemed a *cancel* if the patient is removed from the study for any reason before any study treatment is given. On-Study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary

13.4 If the patient meets criteria for a major bleed, they will have met a major safety endpoint and will be removed from the study. All data up until the point of major bleed should be entered. The patient will then be managed as appropriate per the clinical situation and current guidelines.

13.5 If the patient meets criteria for a recurrent venous thromboembolic event, they will have met a major secondary endpoint and will be removed from the study. All data up until the point of a recurrent venous thromboembolic event should be entered. The patient will then be managed as appropriate per the clinical situation and current guidelines.

13.6 If the patient suffers a non-major clinically relevant bleeding event, they will have met a major safety endpoint. Medical management will be provided in accordance with the location and severity of the bleeding event. This may include temporary cessation of study medication. Once the bleeding event has been appropriately managed, they will restart study medication and will be followed appropriately per protocol. They will not be removed from the study for this event.

13.7 Disease progression is not a reason for stopping the study medication. If the patient goes on hospice, they may continue the study medication and the protocol procedures. If it is decided that the patient is too ill to stay on the study, then it can be stopped.

14.0 Body Fluid Biospecimens – Not applicable

15.0 Drug Information

15.1 Apixaban (Eliquis®) IND #134645

Review the investigator brochure, available on the ACCRU web site, for the most current and complete adverse event information.

15.11 Background: Apixaban (Eliquis) is an oral direct factor Xa inhibitor which impairs coagulation by inhibiting the conversion of prothrombin to thrombin. It does not require antithrombin for antithrombotic activity and inhibits both free and clot-bound FXa. Apixaban has an apparent half-life of about 12 hours and thus is dosed twice-daily. Bioavailability is approximately 50% after oral dosing with maximum concentrations at 4 hours post ingestion. The pharmacokinetics are linear and plasma protein binding in humans is high at nearly 90% with a volume of distribution of approximately 20 liters. Apixaban is metabolized in the liver mainly via the CYP3A4 pathway. Renal excretion accounts for about 27% of total clearance. Approximately 25% of the drug is eliminated in the feces. This drug is not dialyzable due to its high plasma protein binding. Apixaban is currently FDA approved for prevention and treatment of venous thromboembolism and stroke prevention in the setting of non-valvular atrial fibrillation.

15.12 Formulation: Apixaban (Eliquis®) tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban. Both tablets have the appearance of Reddish brown, plain, oval shaped, shallow biconvex film coated tablets.

15.13 Preparation and storage: Store at room temperature 2°C to 30°C (36°F-86°F). Please see current investigator brochure.

15.14 Administration: Apixaban will be provided in bottles containing 200 tablets of either 2.5 mg or 5 mg.

Administer without regard to meals. If patient is unable to swallow whole tablets whole, 2.5 or 5 mg tablets may be crushed and suspended in water, 5% dextrose in water (D5W), apple juice, or apple puree and promptly administered orally. Crushed apixaban tablets are stable in water, D5W, apple juice and apple puree for up to 4 hours. Tablets may also be crushed and suspended in 60 mL of dextrose 5% in water followed by immediate delivery through a nasogastric tube.

15.15 Appearance:
Study drug allocation will be blinded and could be to either apixaban 2.5 mg dose or 5 mg dose. Both doses will be blinded by the company such that neither the investigator nor the patient will know which tablet strength they are using.

15.16 Pharmacokinetic information:
a) Absorption – Time to peak after oral administration is 3 to 4 hours; bioavailability is approximately 50% for doses up to 10 mg.
b) Distribution – Plasma protein binding in humans is approximately 87%. The steady-state volume of distribution is approximately 21 L.
c) Metabolism – Hepatic predominantly via CYP3A4 and to a lesser extent via CYP1A2, 2C8, 2C9, 2C19, and 2J2; substrate of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP)
d) Excretion – Urine (27% as parent drug); feces
e) Half-life Elimination – approximately 12 hours

15.17 Potential drug interactions: Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
Avoid concomitant use with dual strong CYP3A4 and P-glycoprotein inhibitors (eg, clarithromycin, ketoconazole, itraconazole, ritonavir).
Anticoagulants: Apixaban may enhance the anticoagulant effect of other Anticoagulants. *Risk X: Avoid combination*
Combination with fibrinolytics increases the risk of bleeding.
Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.) may enhance the adverse/toxic effect of Apixaban. Specifically, the risk for bleeding may be increased. *Risk C: Monitor therapy*
CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*
CYP3A4 Inducers (Strong): May decrease the serum concentration of Apixaban. *Risk X: Avoid combination*
CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4

Substrates. *Risk C: Monitor therapy*
CYP3A4 Inhibitors (Strong): May increase the serum concentration of Apixaban. Management: Apixaban U.S. prescribing information states dose reduction criteria that may be applied under some circumstances. See full interaction monograph for details. *Risk X: Avoid combination*
Exceptions: Clarithromycin; Cobicistat; Darunavir; Itraconazole; Ketoconazole (Systemic); Lopinavir; Ombitasvir, Paritaprevir, and Ritonavir; Ritonavir; Saquinavir; Telaprevir. Risk C: Monitor therapy.
Inhibitors of CYP3A4 (Strong) and P-glycoprotein: May increase the serum concentration of Apixaban. Management: US labeling recommends a 50% apixaban dose reduction in patients who would otherwise receive 5 or 10 mg twice daily, and avoiding in patients who would otherwise receive 2.5 mg twice daily. Canadian labeling lists any combined use as contraindicated. *Risk D: Consider therapy modification*.

Grapefruit juice may increase levels/effects of apixaban. Management: Advise patients who consume grapefruit juice during therapy to use caution; monitor for increased effects (eg, bleeding).

15.18 Known potential toxicities:

Consult the current investigator brochure for the most current and complete information.

Adverse effects by frequency:

>10%:

Hematologic & oncologic: Hemorrhage (1% to 12%; major: ≤3%; clinically relevant non-major bleeding: 2% to 4%)

1% to 10%:

Endocrine & metabolic: Increased gamma-glutamyl transferase (≤1%)
Gastrointestinal: Nausea (3%)
Hematologic & oncologic: Anemia (3%), bruise (1% to 2%), Post-procedural hemorrhage (≤1%)
Hepatic: Increased serum transaminases (≤1%)

<1% (Limited to important or life-threatening):

Anaphylaxis, gastrointestinal hemorrhage, hematuria, hemophthalmos, hypersensitivity, hypotension, incision site hemorrhage, increased serum alkaline phosphatase, increased serum AST, increased serum bilirubin, intracranial hemorrhage, muscle hemorrhage, perioperative blood loss, postoperative hematoma (incision site), rectal hemorrhage, syncope, thrombocytopenia, wound secretion

15.19a Drug procurement: Bristol Myers-Squibb will supply apixaban labeled for investigational use to Biologics, Inc.

Each participating ACCRU treating location will order a starter supply of blinded apixaban 5mg/apixaban 2.5mg from Biologics. Fax the Drug Order Request Form (found in the forms packet) to the following:

ACCRU Registration Office personnel will monitor the supply of blinded apixaban at each participating location and will arrange for Biologics to send additional supplies, as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19b Nursing guidelines

- Warn patient to avoid taking medication with any other agents (i.e., aspirin, NSAIDS, etc.).
- Warn patients of risk of bleeding, including serious life-threatening internal bleeding.
- Patients may bruise easily. Instruct patients to report excessive bruising to study team.
- Rarely patients may have nausea;, treat symptomatically and monitor for effectiveness.
- Patients should be instructed to let all providers know they are taking medication especially prior to any surgical/invasive procedure.
- Patients should be instructed to avoid agents that utilize the CYP3A4 pathway. Instruct patients to contact the study team prior to starting any new medications.
- Rarely LFTs may increase; monitor LFTs per protocol.

16.0 Statistical Considerations and Methodology

16.1 Sample Size Determination

The primary objective of this study is to determine whether apixaban 2.5 mg twice daily has less bleeding (major bleeding plus clinically relevant nonmajor bleeding) compared to apixaban 5 mg twice daily for secondary VTE prevention in patients with active cancer, previously confirmed deep-vein thrombosis (DVT) or pulmonary embolism (PE) for which they have completed at least 6 months (but no more than 12 months) of anticoagulant therapy. Important assumptions include both clinical and trial observation that bleeding rates in cancer patients with VTE are higher than non-cancer patients. As such, a recent meta-analysis of cancer patients treated with direct factor inhibitors showed that rates of major bleeding were 3.2% and clinically relevant non-major bleeding 14.5% (19). This would equate to rates of 17.7% for these combined outcomes.

The trial is designed as a two-arm, double-blind, randomized study. Patients will be randomized at a 1:1 ratio to receive either 5 mg or 2.5 mg of apixaban twice daily. Assuming the combined bleeding event rate is 9% in the 2.5 mg arm, and 18% in the 5 mg arm, a sample size of 352 (176 per arm) will give us approximately 70% power to detect a difference between the two arms (using a two-sample comparison of proportions with a two-sided alternative at a 5% significance level). The sample size is inflated by 5% to a total of 370 (185) to account for ineligibility and cancellation. We anticipate accruing 15 patients per month to this trial. Based on this accrual rate, we anticipate the trial will complete accrual in 24 months. With the last patient accrued followed for 12 months , the primary analysis will be conducted approximately 36 months after the trial opening. The sample was calculated using EAST 6.3 (Cytel Inc.).

16.2 Primary Hypothesis:

We hypothesize that apixaban 2.5 mg twice daily is associated with a significantly lower combined rate of major bleed plus clinically relevant nonmajor bleed compared to apixaban 5 mg twice daily for the secondary prevention of VTE in patients with active cancer and confirmed deep-vein thrombosis (DVT) or pulmonary embolism (PE) who have completed at least 6 months (but no more than 12 months) of anticoagulant therapy.

16.21 Primary Safety Analysis:

All patients who received at least one dose of either apixaban 2.5 mg or apixaban 5 mg will be included in the primary analysis. Patients will be analyzed according to the drug they received because this is a safety analysis rather than an efficacy analysis. The analysis of major bleeding plus clinically relevant nonmajor bleeding events will primarily focus on those events which occurred during treatment or within 7 days of treatment discontinuation. Major bleeding events observed later will be described separately.

It should be noted that this study is powered for our primary analysis, in which the proportion of patients experiencing at least one bleeding event within 12 months of beginning treatment will be compared across the two study arms using a two-sample comparison of proportions with a one-sided alternative at a significance level of 5% (i.e. a “Z” test).

Though **not part of the primary analysis**, a number of additional analyses of the primary endpoint will also be performed to further explore the data. These should be viewed as additional secondary analyses. In particular, frequency of major bleeding and clinically relevant non-major bleeding will be tabulated by treatment arm. Incidence of major bleeding and clinically relevant non-major bleeding will be estimated using the cumulative incidence function with death without major bleeding or clinically relevant non-major bleeding and with adverse events that results in termination of treatment (including vascular events) as competing risks. The time to event is defined as the time from randomization to the first occurrence of a major bleeding, a clinically relevant non-major bleeding, death without major bleeding or clinically relevant non-major bleeding, or an adverse events that results in termination of treatment (including vascular events). Patients who were lost to follow-up, who withdrew informed consent before the end of the predefined study duration will be censored at the last day the patient had a complete assessment for study outcomes within the intended

study period. The incidence curves of major bleeding and clinically relevant non-major bleeding will be plottted. The incidence of major bleeding and clinically relevant non-major bleeding will be summarized as a combined endpoint and separate endpoints by treatment arm. The difference in the incidences of the combined endpoint at 6 months and at 12 months between treatment arms will be estimated and tested using a normal approximation of the binomial distribution. All tests will be conducted at the one-sided 0.05 significance level.

The incidences of death due to cancer or other causes (without major bleeding or clinically relevant non-major bleeding) and adverse events that result in termination of treatment will be estimated and compared using the same approach.

A sensitivity analysis for these endpoints will be conducted using a stratified (by stratification factors listed in Section 5.0) Cox model adjusting for baseline covariates including location of DVT, renal clearance, age, sex, mobility at randomization, pulmonary disease, and cardiac disease.

16.22 Secondary Safety Analysis:

A secondary safety analysis of the primary safety endpoint will be performed on an intent-to-treat basis using the same approach described in Section 16.21. In addition, we will compare proportion of patients who experience at least one bleeding event (i.e. the primary endpoint) within 6 months of beginning treatment across the two study arms. As with the primary analysis, this will be done using a two-sample comparison of proportions with a one-sided alternative at a significance level of 5%.

16.23 Secondary Efficacy Analysis:

For the secondary efficacy analysis, the time to the first event of the composite DVT/PE outcome will be analyzed using the same method described in Section 16.21. For this outcome, death without DVT/PE and adverse events leading to termination of treatment will be treated as the competing risks.

16.3 Handling of Missing Data:

Monitoring and auditing procedures should be followed, in order to comply with Good Clinical Practice (GCP) guidelines. Each center will be audited at regular intervals to ensure compliance with the protocol, GCP and legal aspects. This will include on-site checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

16.4 Interim Analysis and Study Monitoring:

No formal interim analysis is planned. Risk-benefit will be evaluated by the Mayo Clinic Data Safety and Monitoring Board (DSMB), which will give regular recommendation to the executive committee. Early termination of accrual will be considered if there is evidence of a significant difference in major bleeding rates between the comparators. Access to interim tabular risk benefit data will be restricted.

16.5 Adverse Event Stopping Rule:

The stopping rule specified below is based on the knowledge available at study development. We do note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events that the study team considers to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy the following:

- If 5 or more patients in the first 20 treated patients of either of the study arms (or 20% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related" to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

17.0 Pathology Considerations/Tissue Biospecimens – Not applicable

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

NOTE: Access the RAVE system through the iMedidata portal at [redacted] All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On Study	
Laboratory Tests and Results: Baseline	
Patient Status: Baseline	
Concomitant Medications	
Off Treatment	Submit ≤1 week after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	**Active Monitoring Phase** (Compliance with Test Schedule Section 4.0)	
	At each monthly evaluation during treatment	At end of treatment
Treatment (Intervention)	X	X
Treatment (Intervention): Dose Omissions	X	X
Recurrent Thromboembolism	X	X
Adverse Events: Solicited	X	X
Adverse Events: Other	X	X
Non-CTCAE Bleeding Grading	X	X
Concomitant Medications	X	X
Patient Status: Treatment	X	
Off Treatment		X
ADR/AER	At each occurrence (see Section 10.0)	
Deviation	At each occurrence (see Section 10.0)	

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: none.

19.3 Other budget concerns: The study drug, apixaban (2.5 mg or 5 mg), will be supplied free of charge by Bristol Myers-Squibb.

20.0 References

1. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160(6):761-768.
2. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, B¨ uller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000; 18(17):3078-3083.
3. Hansson PO, S¨orbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med. 2000;160(6):769-774.
4. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med. 2000;160(22):3431-3436.
5. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484-3488.
6. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004; 117(1):19-25.
7. Descourt R, Le Gal G, Couturaud F, et al. Recurrent venous thromboembolism under anticoagulant therapy: a high risk in adenocarcinoma? Thromb Haemost. 2006;95(5): 912-913.
8. Heit JA, Lahr BD, Petterson TM, Bailey KR, Ashrani AA, Melton LJ III. Heparin and warfarin anticoagulation intensity as predictors of recurrence after deep vein thrombosis or pulmonary embolism: a population-based cohort study. Blood. 2011;118(18):4992-4999.
9. Trujillo-Santos J, Ruiz-Gamietea A, Luque JM, et al; RIETE Investigators. Predicting recurrences or major bleeding in women with cancer and venous thromboembolism. Findings from the RIETE Registry. Thromb Res. 2009;123(Suppl2): S10-S15.
10. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JR, Wells P, Woller SC, Moores L. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315-52.
11. Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost. 2000;84(5):805-810.
12. Elting LS, Escalante CP, Cooksley C, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. Arch Intern Med. 2004;164(15):1653-1661.
13. Gross CP, Galusha DH, Krumholz HM. The impact of venous thromboembolism on risk of death or hemorrhage in older cancer patients. J Gen Intern Med. 2007;22(3):321-326.

14. Ru´ız-Gim´enez N, Su´arez C, Gonz´ alez R, et al; RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. Throm Haemost. 2008;100(1):26-31.
15. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, Wong T, Cook R, Solymoss S, Poon MC, Raskob G; LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119:1062-72.
16. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, Imberti D, Mascheroni D, Bucherini E, Gallucci P, D'Alessio A, Prantera T, Spadaro P, Rotondo S, Di Micco P, Oriana V, Urbano O, Recchia F, Ghirarduzzi A, Lo Coco L, Mancuso S, Casuccio A, Rini GB, Siragusa S.Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. J Clin Oncol. 2014 Nov 10;32(32):3607-12.
17. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; the AMPLIFY Investigators. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med. 2013 Aug 29;369(9):799-808.
18. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):699-708.
19. Vedovati MC, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer: A systematic review and meta-analysis. Chest 2015; 147:475-483.
20. Chee CE, Ashrani AA2, Marks RS3, Petterson TM4, Bailey KR4, Melton LJ 3rd5, Heit JA6. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood. 2014; 123:3972-8.
21. Schulman S, and Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692-694.

Appendix I
Model Consent Form

ACCRU Informed Consent Template for Cancer Treatment Trials

(English Language)

***NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for ACCRU model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is [redacted]
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at [redacted] to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

ACCRU-SC-1601, A Phase III, Randomized, Controlled, Double-Blind Study Evaluating the Safety of Two Doses of Apixaban for Secondary Prevention of Cancer Related Venous Thrombosis in Subjects Who Have Completed at Least Six months of Anticoagulation Therapy

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have received treatment for cancer and will also be receiving treatment for a blood clot, deep vein thrombosis or pulmonary embolism.

Why is this research study being done?

It is known that having cancer and receiving treatment for cancer can cause side effects, such as blood clots. The purpose of this research study is to **c**ompare the effects, good and/or bad, of two different doses of apixaban (Eliquis®) *2.5 mg or 5 mg* on you and your blood clot, to find out which is better in preventing and treating blood clots. In this study, you will get either apixaban 2.5 mg or 5 mg twice daily. You will not get both.

How many people will take part in the research study?

About 370 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study treatment

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam (including weight and height, and a rating of how well you perform activities of daily living)
- Routine blood tests
- Pregnancy test if you are a woman of childbearing potential
- Current list of medications

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular care for cancer or for blood clots.

- Medical history and physical exam (including weight and height, and a rating of how well you perform activities of daily living)
- Evaluation of symptoms/side effects
- Current list of medications

During the study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance, as in the flip of a coin. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. Neither you nor your doctor will know which dose of apixaban you will receive. You have an equal chance of being placed in either group.

If you are in group 1, you will receive the study drug apixaban. This is a pill and you will take 2.5 mg by mouth twice a day for 12 months. Every 30 days you will visit your study doctor for a short follow-up visit that will include the following:

- Height;
- Weight;
- A check to see if you are having any side effects from the study medication;
- A review of all medications you are currently taking in addition to the study medication.
- **Bleeding assessment**: You will be asked questions about any bleeding you have experienced.

If you are unable to visit your study doctor, a member of the study team will contact you by phone every 30 days to ask about the items listed above.

If you are in group 2, you will receive the study drug apixaban. This is a pill and you will take 5 mg by mouth twice a day for 12 months. Every 30 days you will visit your study doctor for a short follow-up visit that will include the following:

- Height;
- Weight;
- A check to see if you are having any side effects from the study medication;
- A review of all medications you are currently taking in addition to the study medication.
- **Bleeding assessment**: You will be asked questions about any bleeding you have experienced.

If you are unable to visit your study doctor, a member of the study team will contact you by phone every 30 days to ask about the items listed above.

We want to find out if the apixaban 2.5 mg will help to prevent blood clots and reduce the risk of bleeding better than the apixaban 5 mg. You will not know which study drug you will be receiving.

When I am finished taking apixaban for 12 months, what will happen?

At the end of the study treatment period (12 months or 365 days), you can be seen by your doctor to determine whether you should continue to take blood thinners or stop taking blood thinners. If it is

decided that you should continue to take blood thinners, a prescription for the treatment will need to be given to you by your doctor.

The End of Treatment follow-up visit will include the following (NOTE: if you are unable to visit your study doctor, a member of the study team will contact you by phone):

- A check to see if you are having any side effects from the study medication;
- A review of all medications you are currently taking in addition to the study medication.
- Bleeding assessment.

If you cannot complete the treatment because you develop a blood clot or start bleeding, the following tests may be done. This will be up to your doctor. They are part of your regular care for cancer or for blood clots.

- Routine blood tests
- Ultrasound or CT scan

How long will I be in the research study?

You will be asked to take the apixaban for a total of 12 months.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop the study drug safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the apixaban can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. You will be watched carefully for any side effects. However, doctors may not know all the side effects that may happen. Side effects may be mild to very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking apixaban. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study team about any side effects that you have while taking part in the study.

Risks and side effects related to apixaban include those which are:

<u>Likely (>1%)</u>

- Minor bleeding from the nose
- Bruising
- Blood in the urine
- Heavy menstrual bleeding
- Collection of blood under the skin

- Coughing up blood
- Rectal bleeding
- Gum bleeding

Rare but serious (≥ 0.1% to < 1%)

- Serious bleeding from the stomach or intestines
- Throwing up blood
- Serious bleeding into the eye
- Serious bleeding around the heart
- Serious bleeding into the muscles
- Allergic reactions to drug including low platelet count or liver damage
- Bleeding that causes death
- Abnormal or longer than normal vaginal bleeding
- Serious blood loss causing damage to internal organs

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use effective birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope the study drug will be more useful in preventing and treating blood clots in cancer patients, compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the study drug to try to prevent and/or treat blood clots. This information could help future patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer related blood clot.

Your other choices may include:

- Getting treatment or care for your cancer-related blood clot without being in a study
- Taking part in another study
- Getting no treatment

Because blood clots are serious and potentially dangerous, it is important to discuss all treatment options with your doctor. Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Academic and Community Cancer Research United (ACCRU)
- Mayo Clinic Rochester
- Bristol Myers-Squibb
- Institutional Review Boards (IRB) or Ethics Committees (committees that have reviewed this study to help ensure the study is conducted in a safe and ethical manner, and that the rights of study participants are respected).

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of study results. You can search this web site at any time.

Tests done at hospitals or clinics other than the study clinic

If you have blood tests or other medical tests such as scans or x-rays at a clinic or hospital other than to the study clinic *[insert name of institution]*, your study doctor may need to review results of these tests as they relate to this study.

Please read the following statements and mark your choice:

I permit _____ *[investigator's name(s)]* to obtain medical information from my primary care giver _____*[primary caregiver's name(s)]*as it relates to this study. This may include information regarding any blood tests, x-rays or scans:

☐ Yes ☐ No Please initial here:_____ Date:_____

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans may not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agent, apixaban, will be provided free of charge while you are taking part in this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted]. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call [redacted] and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You may also visit the NCI Web site at [redacted]

- For NCI's clinical trials information, go to: [redacted]
- For NCI's general information about cancer, go to [redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Appendix II
Strong CYP3A4 Inhibitors/Inducers

	Strong CYP3A4 Inhibitors	**Strong CYP3A4 Inducers**
Antibiotics	Clarithromycin Telithromycin	Rifampin Rifabutin
Antidepressants	Nefazodone	
Antifungals	Itraconazole Ketoconazole	
Protease Inhibitors	Posaconazole Voriconazole Atazanavir Boceprevir Darunavir Delavirdine Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	
Anticonvulsants		Carbamazepine Phenobarbital Phenytoin Fosphenytoin Primidone
Other		St John's wort

Appendix III
Khorana Score

The Khorana score is a simple validated risk model for predicting rates of VTE in cancer outpatients receiving chemotherapy, using baseline clinical and laboratory variables. This risk model incorporates five predictive variables for VTE including: site of cancer (2 points for very high-risk site; 1 point for high risk site), platelet count ≥ 350 x 109/L (1 point), hemoglobin < 10 g/dL and/or use of erythropoiesis stimulating agents (1point), leukocyte count > 11x109/L (1 point), and body mass index ≥ 35 kg/m2 (1 point) (1). Based on their score, patients are then divided into low (0 points), intermediate (1 -2 points) or high risk (≥ 3 points). Rates of venous thromboembolism over the ensuing 2.5 months were 0.3 - 0.8% in low-risk, 1.8 - 2% in intermediate-risk, and 6.7-7.1% in high-risk groups.

Very high risk sites include stomach and pancreas cancers. High risk cancer sites include lung, lymphoma, gynecologic, bladder, and testicular cancers.

Risk assessment can be promptly carried out using an online calculator:
[redacted]

Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008 May 15;111(10):4902-7.

Appendix IV
Non CTCAE Bleeding Grading Scale
Based on The International Society on Thrombosis and Haemostasis (ISTH) guidelines

Grade	Symptom
1	**Minor bleed** Minor bleeding is defined as overt bleeding that did not meet criteria for major bleeding or clinically relevant non-major bleeding.
2	**Non-Major bleed** Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with a member of the health care team, or temporary cessation of study treatment.
3	**Major bleed** Major bleeding is defined as overt bleeding plus a hemoglobin decrease of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red blood cells, or intracranial, intraspinal, intraocular, retroperitoneal, pericardial or fatal bleeding.

Appendix V
Phone Contact Sheet
Telephone Script

Protocol Title: A Phase III, Controlled, Randomized, Double-Blind Study Evaluating the Safety of Two Doses of Apixaban for Secondary Prevention of Cancer Related Venous Thrombosis in Subjects Who Have Completed at Least Six Months of Anticoagulation Therapy
IRB #:
Principal Investigator: Robert McBane, MD

"Good morning/afternoon. This is _____ calling from [name of institution].
May I speak to_____?"
(If participant is there proceed to the following:)

"I would like to ask you a few questions regarding your blood thinner medication**, apixaban and** the clinical trial in which you have been enrolled. This will allow us to gather very important information about the safety and benefit of using this medication in treating and preventing blood clots."

"I would like to ask these questions related to our study after confirming your name"
Patient Name _____

1. Over the past month, have you missed any doses of your blood thinner medication?
   ____ Yes
   If yes, approximately how many doses do you estimate that you have missed? _____
   If yes, why was the dose missed? _____
   ____ No, I have not missed any doses of medication

2. Over the past month have you had another blood clot problem?
   ____ Yes, a DVT (must contact local medical doctor to obtain documentation)
   ____ Yes, a PE
   ____ Yes, both a DVT and a PE
   ____Yes, something else (e.g. an arterial clot). Please describe: _____
   ____ No, I have not had any more clots.

3. While you have been taking this medication as recommended have you experienced any major bleeding which required hospitalization or blood transfusion?
   ____ Yes. Please describe_____
   ____ No

   Any bleeding other than that from an injury? (For example a spontaneous bloody nose.)
   ____ Yes, Please describe_____
   ____ No

4. Over the past month, have you undergone any surgeries or invasive procedures?
   ____ Yes
   If yes, what type of surgery/procedure did you have? _____
   What was the date of the procedure? __ __-___ ___-___ ___ (MM-DD-YY)
   ____ No, I have not had any surgeries or procedures

5. Which of the following best applies to your current activity rating: _____
   A. Fully active, able to carry on all activities before your disease without restriction
   B. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
   C. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
   D. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
   E. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

6. What is your current weight? _____

7. Have you started any new medications? List these _____

8. Have you had any new leg swelling?
   ___ Yes
   i. If yes, suggest that the patient see their medical provider
   ____No, I have not had any new leg swelling.

9. Have you had any new chest pain or shortness of breath?
   ___ Yes
   i. If yes, instruct the patient to call 911/go to ER.
   ___ No, I have not had any new chest pain or shortness of breath.

Do you have any questions for me?

"Thank you for participating in our study.

NOTE: If there is any evidence of bleeding or clotting, review this with the attending clinician and **obtain documentation from the local healthcare provider if patient gave consent.**

Appendix VI
Patient Education Material

Deep Vein Thrombosis and Pulmonary Embolism
(©2016 Mayo Foundation for Medical Education and Research)
See next page

Appendix VII

Patient Compliance Information

1. Over the past month, have you missed any doses of your blood thinner medication?
   ____ Yes,
   ____ If yes, approximately how many doses do you estimate that you have missed?
   ____ If yes, why was the dose missed?
   ____ No, I have not missed any doses of medication