Protocol Title: Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)

Protocol Short Title: CANVAS: Cancer-related VTE Anticoagulation Strategies

NCT #: NCT02744092

Updated: January 20, 2021

Supplement 1

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ALLIANCE FOUNDATION TRIALS, LLC (AFT)

PROTOCOL NUMBER
AFT-28

Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)

CANVAS: Cancer-related VTE Anticoagulation Strategies

Protocol Version: #7
Protocol Version Date: January 20, 2021

ClinicalTrials.gov Identifier: NCT02744092

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This study does **not** involve any investigational new drugs/agents/devices (no INDs).

Drugs used in the study are all commercially available:

Warfarin (Coumadin®)	Rivaroxaban (Xarelto®)
Dalteparin (Fragmin®)	Apixaban (Eliquis®)
Enoxaparin (Lovenox®)	Edoxaban (Savaysa®)
Fondaparinux (Arixtra®)	Dabigatran (Pradaxa®)

PROTOCOL SIGNATURE PAGE

Protocol Title:	Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)
Protocol Number:	AFT-28
Protocol Version/ Date:	January 20, 2021
Sponsor Name:	Alliance Foundation Trials, LLC

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, all applicable regulations, ICH Good Clinical Practice (GCP) and Declaration of Helsinki.

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First Name, Last Name	Date, Signature

CANVAS Trial (AFT-28) Resources

Contact with QUESTIONS:	
Primary contact for questions about: • Patient eligibility • Drug administration • Protocol treatment • Dose modifications	Study Chair Deb Schrag MD **617-582-8301, Deb_schrag@dfci.harvard.edu*** Study Chair Jean Connors MD **617-525-9337, jconnors@bwh.harvard.edu*** *CC: CANVAS_Coordinator@dfci.harvard.edu
Primary contact for questions about: • Site activation • Protocol document • Consent form • Regulatory issues • Site Zone (online Electronic Master File) • Site reimbursement	AFT-28 Project Manager **CANVAS@AllianceFoundationTrials.org**
Primary contact for questions about: • Patient enrollment • Patient questionnaire administration • REDCap (online electronic data capture application) • Forms completion (CRFs) • Adverse event reporting • Submission of study data	Central Study Coordinator **617-632-4490** **CANVAS_Coordinator@dfci.harvard.edu**

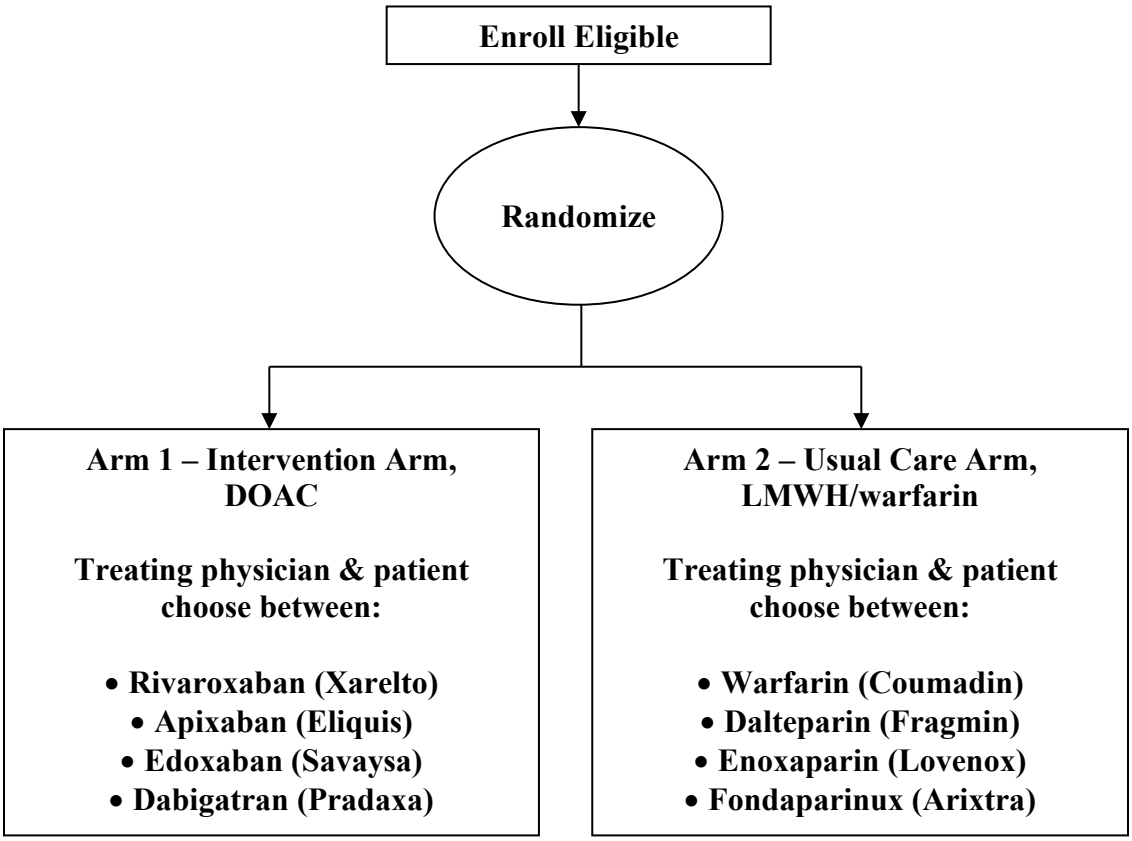
SYSTEMS USED for this study:	
Site Zone is where you will: • Upload and submit the required documents for **site activation** for this study. • Find the most up-to-date study documents, such as protocol, model informed consent form, tip sheets, etc.	**https://sitezone.mywingspan.com/sitezone/#/trials** For Site Zone help: TechSupport@AllianceFoundationTrials.org
Site Protocol Training: • Watch the virtual training videos.	The protocol training for **study staff** can be found here (15-minute video): https://vimeo.com/310853060/83ed78f342 The protocol training for **physicians** can be found here (9-minute video): https://vimeo.com/310855828/43624a2713
REDCap used to: • Enroll/randomize patients. • Enter all study data/case report forms (CRFs). • Report reportable adverse events.	**https://redcap.partners.org** For REDCap help: Central Study Coordinator, 617-632-4490 CANVAS_Coordinator@dfci.harvard.edu

CANVAS Trial (AFT-28) Synopsis

Study Title	Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)
Study Number	AFT-28
Sponsor	Alliance Foundation Trials, LLC (AFT)
Funding	This trial is supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-1503-29805).
Study Type/Phase	Randomized Effectiveness Trial
Clinical Indication	VTE (venous thromboembolism) associated with cancer
ClinicalTrials.gov Identifier	NCT02744092
IND Number	None, no IND
Number of Trial Patients	811 study-wide ***(Note: This is the final N.)***
Estimated Duration of Trial	3.5 years
Acronyms used througout the protocol	**AFT** - Alliance Foundation Trials, LLC **VTE** - Venous Thromboembolism **DVT** - Deep Vein Thrombosis **PE** - Pulmonary Embolism **LMWH** - Low Molecular Weight Heparin **DOAC** - Direct Oral Anticoagulants
Rationale	Cancer patients are at risk for VTE (venous thromboembolism). Anticoagulation therapy is necessary to prevent recurrent VTE. Current practice patterns are a hybrid use of LMWH+/-warfarin. Recently, the FDA has approved 4 Direct Oral Anticoagulants (DOACs) for VTE based on efficacy trials showing non-inferiority to warfarin. Given the myriad exclusion criteria present in efficacy trials, **the effectiveness of DOACs in cancer is unknown**.
Objectives	**Objective 1:** To compare the effectiveness of anticoagulation with a DOAC (intervention) with LMWH/warfarin (comparator) for preventing VTE recurrence in patients with cancer. **Objective 2:** To compare the harms of DOAC vs. LMWH/warfarin therapy for cancer patients with VTE based on the cumulative rate of major bleeding at 6 months. **Objective 3:** To compare the impact of DOAC vs. LMWH/warfarin therapy on the experience and burden of anticoagulation therapy for cancer patients with VTE. **Objective 4:** To compare the impact of DOAC vs. LMWH/warfarin therapy on mortality in cancer patients with VTE.

Trial Design	The study design is a **randomized effectiveness study** to evaluate the effectiveness of DOAC therapy compared to usual care with LMWH/warfarin. Participants who decline randomization will be offered the opportunity to participate in the preference cohort.** This is a hybrid design that consists of both a randomized cohort and a preference cohort.** Eligible patients who accept randomization will be enrolled in the study (**the randomized cohort**), and they will be randomly assigned to either the DOAC therapy group (Arm 1) or the usual care group (Arm 2).** Those patients who decline randomization but choose treatment on one of the two study arms (Arm 1 or Arm 2) will be enrolled to the study (**the preference cohort**).** See the "Statistical Considerations" section of this protocol for complete details. ****The randomized cohort closed to new enrollment in April, 2020. Based on the results of monthly data monitoring performed June 2017, the preference cohort is CLOSED to new enrollment following the closing rule specified in the protocol.****
Eligibilty Criteria	Can be found here: 4.0 Patient Selection / Eligibility Criteria
Protocol Treatment	Arm 1: Intervention arm, DOAC Arm 2: Usual care, LMWH/warfarin This effectiveness study will not provide any drugs because all drugs are commercially available, FDA-approved, and are being prescribed on-label. Drugs should be billed to the patient's insurance company or to the patient as your site does for any other standard medication. Drugs should be prescribed to the patient as your site does for any other standard medication.

Schema


Enroll Eligible
Randomize
Arm 1 – Intervention Arm, DOAC
Treating physician & patient choose between:
• Rivaroxaban (Xarelto)
• Apixaban (Eliquis)
• Edoxaban (Savaysa)
• Dabigatran (Pradaxa)
Arm 2 – Usual Care Arm, LMWH/warfarin
Treating physician & patient choose between:
• Warfarin (Coumadin)
• Dalteparin (Fragmin)
• Enoxaparin (Lovenox)
• Fondaparinux (Arixtra)

AFT-28 Protocol Table of Contents

1.0 BACKGROUND

Venous Thromboemboli (VTE) are common, often lethal and a major public health threat A deep venous thrombosis (DVT) is a blood clot in a large vein, usually in the leg or pelvis. Patients often note swelling, pain or redness in one leg. Sometimes a DVT detaches from its site of formation and mobilizes in the blood stream. If the clot travels through the heart to the lungs, it can suddenly block an artery supplying the lungs. This event is called a pulmonary embolism (PE). PE symptoms include shortness of

breath, chest pain, and rapid heart rate. Each year in the US, an estimated 600,000–900,000 people develop VTE, and more than 100,000 die, many suddenly.[1-4] Because people who survive a first VTE are at extremely high risk for another episode, a main treatment goal is to prevent a second event.

Multiple pathophysiologic mechanisms put cancer patients at excess risk for VTE A cancer diagnosis is one of the strongest predisposing risks for VTE. VTE is sometimes the first manifestation of cancer. The excess VTE risk in cancer stems from three interrelated pathogenic mechanisms: 1) hypercoagulability; 2) stasis or slow blood flow; and 3) vascular injury to blood vessel walls. Tumor features such as histology (adenocarcinoma), site (pancreatic, kidney, uterus) and extent of disease increase risk. Certain chemotherapy agents, hormonal therapy, the use of indwelling catheters, surgery, hospitalization and immobility all increase risk and contribute to the high frequency of VTE in cancer patients.

VTE is a frequent distressing complication of cancer and is associated with high mortality Two population-based case control studies demonstrate that cancer increases the risk for VTE by 4 to 7 times and is the second leading cause of death in oncology patients.[5, 6] Approximately 20% of all VTEs occur in cancer patients. A recent study showed that 12.5% of chemotherapy recipients in ambulatory practice developed a VTE within 12 months.[7] The rate varied from 8% to 19% depending on cancer type. In contrast, the VTE rate was only 1.4% for age and gender matched cancer-free controls from these practices.[8] Cancer patients with VTE have more advanced disease, worse performance status and higher risk of death. Although much of the excess is due to cancer itself, a significant proportion is due to recurrent VTE.[1]

Anticoagulation therapy is necessary to prevent recurrent VTE Cancer patients face very high risks of recurrent VTE particularly if they have high tumor burden or are receiving chemotherapy.[9] Therefore, absent a major contraindication such as ongoing/active bleeding, very low platelet count, and/or large brain metastases, anticoagulation is indicated for cancer patients following VTE. This is true whether the VTE is symptomatic or an incidental finding detected on an imaging study. Practice guidelines recommend that advanced cancer patients continue anticoagulant therapy long-term since the risk of VTE persists indefinitely.

Warfarin is the mainstay of anticoagulation treatment to prevent VTE but requires close monitoring Warfarin is an oral medication often known by its brand name, Coumadin. It prevents the formation of blood clots and their migration. The FDA approved it in 1954 when found to prevent blood clots, and its use remains ubiquitous. Despite its effectiveness, treatment with warfarin has major shortcomings. Its therapeutic window is narrow. Too little warfarin fails to protect against VTE. Too much leads to an excess risk of bleeding. There is great variability in its metabolism, and it interacts with some foods and many medications. Therefore, close monitoring is required. This entails blood testing, often weekly, to ensure that the international normalized ratio (INR) is within therapeutic range. Warfarin therapy is especially challenging for cancer patients for two reasons. First, cancer patients take many medications which can either accelerate or impede warfarin metabolism. Second, warfarin has to be reversed prior to surgical procedures. This takes about 5 days and requires multiple blood draws.

Low Molecular Weight Heparins (LMWHs) Are the Guideline Sanctioned Approach for Treating VTE in Cancer For many years, the management of VTE consisted of several days of inpatient treatment with intravenous heparin followed by transition to oral warfarin. Because of unfractionated heparin's short half-life and metabolism, it required close monitoring and intravenous treatment. In the1990s, the LMWHs (e.g., dalteparin (Fragmin) and enoxaparin (Lovenox)) were developed.[10-13] They require subcutaneous injection but no blood monitoring. In 2003, the CLOT study demonstrated that in patients with malignancy and VTE, dalteparin was more effective than warfarin at reducing VTE recurrence (LMWH: 9%, warfarin: 17%) with similar bleeding rates.[14] On this basis, LMWH therapy became the

preferred regimen.[7, 15-17] A Cochrane review of anticoagulation to prevent recurrent VTE in cancer found that recurrent VTE hazard was 0.47 (95% CI 0.32-0.71) for LMWH vs. warfarin with no major differences in bleeding, survival or other complications.[14]

Anticoagulation therapy with either LMWH or warfarin is complex and often burdensome Notwithstanding its superior efficacy to warfarin and guideline endorsements, adherence to LMWH therapy is challenging because it requires daily injections. Patients encounter problems preparing syringes, injecting needles and with bruising. In order to undergo surgical procedures including biopsy, endoscopy, or catheterization, warfarin must be stopped a week in advance. To prevent VTE during this period, oncologists prescribe "a LMWH bridge" since LMWH has shorter half-life. After procedures are complete, warfarin can be restarted and LMWH discontinued when warfarin again reaches therapeutic levels, typically after 5 days. Analyses of practice patterns suggest that among cancer patients with VTE: about a third choose LMWH, a third warfarin, and a third opt for LMWH but transition to warfarin within several months when injections become too burdensome. Current oncology practice is thus best described as a *hybrid* strategy.

Direct Oral AntiCoagulants (DOACs) have recently been FDA approved to treat/prevent VTE DOACs (**Table 1**) are a major, recent therapeutic advance for management of VTEs. They are oral but unlike warfarin, do not require intensive monitoring to stay within therapeutic range. Four DOACS have recently been FDA approved.[18-22] Factor Xa activates prothrombin to thrombin and triggers the coagulation cascade to form clot. Thrombin cleaves fibrinogen to fibrin, forming the structure of the clot. Apixaban, edoxaban, and rivaroxaban, directly inhibit Xa. Dabiagatran directly inhibits thrombin. The DOACs were first approved to prevent stroke and embolism in atrial fibrillation and after orthopedic surgery. Each agent has been evaluated in large efficacy trials and shown to be at least as efficacious as warfarin at preventing recurrent VTE and at least as safe in terms of the risk of bleeding.[18, 20, 22-24]

Table 1	**Comparison of DOACs Recently Approved by the FDA**			
Direct Oral Anticoagulants (DOACs)	**Dabiagatran**[21] (Pradaxa)	**Rivaroxaban**[20] (Xarelto)	**Apixaban**[18] (Eliquis)	**Edoxaban**[19] (Savaysa)
FDA approval date for VTE	April 7, 2014	Nov 2, 2012	Aug 21, 2014	Jan 8, 2015
Target factor	II (thrombin)	Xa	Xa	Xa
Renal clearance	80 %	33 %	25 %	35 %
Renal dose modification	Don't use	Not if CrCl<30ml/min	None	30mg if CrCl<50
Hepatic metabolism	Minimal	Yes, CYP3A4	Yes, CYP3A4	Minimal
Liver failure modification	None	Don't use	Don't use	None
Bleeding risk vs. warfarin	same	same/better	better	better

Efficacy trials have evaluated benefits/harms of DOACs for VTE in carefully selected patient groups Table 2 summarizes the large efficacy RCTs comparing the DOACs to a vitamin K antagonist (VKA) (e.g., warfarin). Each demonstrates that VTE recurrence, bleeding and death rates from anticoagulation with a DOAC are non-inferior to rates with VKA. They led the FDA to approve the DOACs for VTE treatment. *Table 2 underscores how few cancer patients were included in these pivotal trials.* A recent meta-analysis showed similar findings for cancer subgroups. For example, the OR for VTE was 0.56 (95% CI 0.27-1.14) for DOAC vs. VKA therapy.[25] Notably, these trials excluded patients with short life expectancy and significant

comorbidities, and in some trials, patients were excluded if they were eligible for treatment with LMWH. As a result of this evidence gap, it is not surprising that practice guidelines from the National Comprehensive Cancer Network[26], the American Society of Clinical Oncology[7, 27], The European Society of Medical Oncology,[16] The American Society of Hematology and the American Thoracic Society[15] advocate neither for nor against DOAC use in cancer. These guidelines all emphasize the need for effectiveness studies and do not definitely recommend for or against use of DOACs versus LMWH/VKA therapy.[28-30]

Table 2: Recent Large RCTs of DOACs vs. Warfarin Have Included Very Few Cancer Patients

					Overall Outcomes: Intervention vs. Control		
RCT Name	Intervention	Control	N	Cancer N (%)	VTE/VTE death	Bleeding/ Bleeding death	Any death
Amplify[18]	Apixaban	VKA	5395	169 (3%)	1.5 vs. 1.9%	4.3 vs. 9.7%	1.5 vs. 1.9%
Einstein-DVT[22]	Rivaroxaban	VKA	3449	207 (6%)	2.1 vs. 3.0%	8.1 vs. 8.1%	2.2 vs. 2.9%
Einstein-PE[20]	Rivaroxaban	VKA	4832	223 (4%)	2.1 vs. 1.8%	10.3 vs 11.4%	2.4 vs. 2.1%
HOKUSAI[19]	Edoxaban	VKA	8240	208 (2%)	3.2 vs. 3.5%	8.5 vs.10.3%	3.2 vs 3.1%
RE-COVER I[21]	Dabigatran	VKA	2539	121 (5%)	2.4 vs. 2.1%	1.6 vs. 1.9%	1.6 vs. 1.7%
RE-COVER II[31]	Dabigatran	VKA	2589	100 (4%)	2.3 vs. 2.2%	1.2 vs. 1.7%	2.0 vs. 1.9%

*AMPLIFY and RE-COVER I & II outcomes are event rates at 6 months; the other study outcomes reflect rates at 12 months

With this background, the rationale for this study is compelling because:

- VTEs occur commonly in cancer patients, can be fatal, and require anticoagulation to prevent recurrence.
- Warfarin has long been the mainstay of VTE treatment but requires careful blood monitoring.
- LMWHs are an alternative but require subcutaneous injection and thus are onerous for patients.
- LMWH prevents recurrent VTE in cancer better than warfarin in some studies but isn't clearly better in terms of safety or survival.
- Longstanding usual practice is a hybrid of LMWH/warfarin with many patients transitioning back and forth between the two. Typically, patients start on a LMWH and transition to warfarin; however, some stay on LMWH for the long term and may transition to warfarin at a later date particularly if chronic self-administration of subcutaneous injections becomes arduous.
- FDA has approved 4 DOACs for VTE based on *efficacy* trials showing non-inferiority to warfarin. These trials have included very few cancer patients leaving an evidence gap.
- Given the myriad exclusion criteria present in efficacy trials, the *effectiveness* of DOACs in cancer is unknown.

2.0 OBJECTIVES

Cancer patients are frequently diagnosed with VTE and need to choose an anticoagulation strategy. Although there are now multiple options, patients and their doctors lack information that clearly balances benefits/harms and burdens so as to inform these choices. To fill this gap, the proposed study has the following goals:

Objective 1: To compare the effectiveness of anticoagulation with a DOAC (intervention) with LMWH/warfarin (comparator) for preventing VTE recurrence in patients with cancer.

Hypothesis: The benefit of secondary prophylactic anticoagulation with a DOAC is not worse than the benefit from treatment with LMWH/warfarin based on cumulative VTE recurrence reported by patients or their clinicians at 6 months.

Objective 2: To compare the harms of DOAC vs. LMWH/warfarin therapy for cancer patients with VTE based on the cumulative rate of major bleeding at 6 months.

Hypothesis: The harms from DOAC therapy are not worse than the harms from LMWH/warfarin therapy based on the cumulative rates of major bleeding reported by patients or clinicians at 6 months.

Objective 3: To compare the impact of DOAC vs. LMWH/warfarin therapy on the experience and burden of anticoagulation therapy for cancer patients with VTE.

Hypothesis 3a: DOAC and LMWH/warfarin therapy are associated with similar overall HRQOL (health-related quality of life) at 3 and 6 months.

Hypothesis 3b: DOAC therapy is superior to LMWH/warfarin based on the Anti-Clot Therapy Scale at 3 and 6 months.

Objective 4: To compare the impact of DOAC vs. LMWH/warfarin therapy on mortality in cancer patients with VTE

Hypothesis: The risks of all cause and cause-specific mortality for cancer patients treated with DOAC therapy are not worse than the risks for those treated with LMWH/warfarin based on survival at 6 months.

3.0 STUDY DESIGN

3.1 Description of study and schema

The study design is a **prospective unblinded two-group randomized effectiveness study** to evaluate the effectiveness of DOAC therapy compared to the usual care with LMWH/warfarin. The study has a hybrid design in that in addition to the randomized cohort, it also includes a preference cohort.** Eligible patients who accept randomization will be enrolled in the study (**the randomized cohort**), and they will be randomly assigned to either the DOAC therapy group (Arm 1) or the usual care group (Arm 2).** Those patients who decline randomization but choose treatment on one of the two study arms (Arm 1 or Arm 2) will be enrolled to the study (**the preference cohort**).** See protocol section **13.0 Statistical Considerations and 18.0 Statistical Analysis Plan** for complete details.

The study intervention, DOAC therapy, has established *efficacy*, but its real world effectiveness in cancer patients is unknown. The study outcomes are measurable and meaningful to patients and their families. Knowledge from this study will help patients and their clinicians make better informed decisions about anticoagulation therapy. To understand the impact of individuals who choose not to be randomized, the study will also track outcomes for patients who consent to report outcomes, but decline randomization.** This hybrid design as well as a well-specified plan for capturing important patient and treatment factors will enable better understanding of the relative risks/harms for individuals with specific features.

****The randomized cohort CLOSED to new enrollment in April, 2020. The preference cohort is CLOSED to new enrollment.**

The protocol schema can be found above.

3.2 Study Completion

The anticipated study completion date (the date by which the last data point for final data analysis is received) is November 15th, 2020. This presumes that no patients are enrolled after May 1st and that 6 month follow up data is complete as of November 1st. Two extra weeks have been added in case it should be necessary to track late assessments. Please note: the official study completion date will be dependent on the date of the last enrolled patient.

4.0 PATIENT SELECTION / ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

4.1.1 Diagnosis of an **advanced** solid tumor, lymphoma, chronic lymphocytic leukemia (CLL), or myeloma (no time restrictions or limitations) **–OR–** diagnosis of **early** stage solid tumor cancer, lymphoma, chronic lymphocytic leukemia (CLL), or myeloma ≤ 12 months prior to study enrollment.

4.1.2 Diagnosis of VTE ≤ 30 days prior to study enrollment for which potential benefits of anticoagulation therapy to prevent recurrence of VTE are felt by the treating physician to exceed the potential harms. Diagnosis may be made based on physical exam or imaging studies. Participants with both symptomatic and asymptomatic VTEs are eligible.

Any anticoagulation drug/strategy may be used to treat the index VTE; protocol treatment will begin ≤ 14 days after enrollment.

4.1.3 Treating physician *intends* to put participant on anticoagulation therapy for at least three months.

4.1.4 Age ≥ 18 years.

4.1.5 Platelet count is ≥ 50,000/mm^3 (≤ 7 days prior to enrollment).

4.1.6 CrCl (Creatinine Clearance) is ≥ 15 ml/min (≤7 days prior to enrollment).

4.2 Exclusion Criteria

4.2.1 Diagnosis of acute leukemia.

4.2.2 Has ever received or is scheduled to receive an **Allogeneic** Hematopoietic Stem Cell Transplantation (alloHSCT).

- Patients who have ever received an **Autologous** Hematopoietic Stem Cell Transplantation (autoHSCT) **are** eligible.

- Patients who are scheduled to receive an **Autologous** Hematopoietic Stem Cell Transplantation (autoHSCT) are **not** eligible.

4.2.3 Ongoing, clinically significant bleeding (CTCAE grade 3 or 4).

4.2.4 Ongoing therapy with a P-gp inhibitor (e.g., nelfinavir, indinavir, or saquinavir-protease inhibitors for HIV) as these drugs interact with the factor Xa inhibitors.

4.2.5 Need for ongoing therapy with: certain antifungals (itraconazole, ketaconazole, voriconazole); rifampin; or certain antiseizure medications (phenytoin, carbamazepine, phenobarbital) at the time of enrollment.

4.2.6 Subjects with any other contraindications to anticoagulation or conditions that as judged by the treating clinician would place the subject at increased risk of harm if s/he participated in the study.

4.2.7 Pregnant or nursing.

4.3 Definitions and answers to FAQs with regard to the eligibility criteria

General:

- Non-English speaking participants are eligible for participation in this study. Sites must follow their local SOPs for consenting non-English speaking participants. Translated materials are currently available in Spanish.

Criterion 4.1.1:

- "Advanced" cancer means stage IV, metastatic, and/or recurrent cancer.
- If diagnosed with advanced cancer, then date of cancer diagnosis can be any date (no time restrictions or limitations).
- "Early stage" cancer means any cancer EXCEPT one that is stage IV, metastatic, and/or recurrent.
- If diagnosed with early stage cancer, then the diagnosis date must be ≤ 12 months prior to the date on which the patient is enrolled on this trial.
- Patients with multiple malignancies **are** eligible as long as other criteria are met.
- DCIS (ductal carcinoma in situ) and MDS (myelodysplastic syndromes) are not eligible.
- Primary CNS (central nervous system) tumors, primary brain tumors, and/or brain metastases are eligible.

Criterion 4.1.2:

- Patients with a history of prior VTE and prior anticoagulation **are** allowed.
- "VTE" means PE,DVT, and/or portal vein thrombosis (any or all are acceptable).
- **VTE stands for Venous Thromboembolism**. A VTE is a blood clot that breaks loose and travels in the blood. DVTs and PEs are types of VTEs.
- **PE stands for Pulmonary Embolism**. A PE is a sudden blockage in a lung artery (often caused by a DVT that breaks loose and travels through the bloodstream to the lung).
- **DVT stands for Deep Vein Thrombosis**. A DVT is a blood clot that forms in a vein deep in the body, often in the leg or pelvis.
- The following types of VTE **are** also eligible: any line associated clot, calf vein, splanchnic, and sub-segmental PE **are** eligible. It is recommended that sites not enroll superficial vein thrombosis unless there is intention to treat with full dose anticoagulation for at least 3 months.
- The VTE diagnosis that makes a patient eligible for this study will be referred to as the "**index VTE**" throughout this protocol.
- **"Recurrent VTE"** is defined as the emergence of venous thrombosis of a site that was either previously uninvolved or had interval documentation of incident DVT or PE resolution.
- **The participant may receive ANY initial anticoagulation therapy for their index VTE.** Protocol treatment will begin ≤ 14 days after study enrollment/randomization.
- "…for which potential benefits of anticoagulation therapy to prevent recurrence of VTE are felt by the treating physician to exceed the potential harms" – this judgment will be made by the treating physician in each patient's case. All anticoagulation strategies used in the course of the study should be used in accordance with FDA-labeling and clinical judgment.
- Patients being treated prophylactically with anticoagulants **are eligible.**
- Patients being treated with anticoagulants at a sub-therapeutic level (i.e., intermediate intensity or intermediate dosing) **are eligible.**
- Patients who have been on standard (i.e., full) intensity anticoagulation and get a new clot **are not eligible.**

Criterion 4.2.3:

NCI CTCAE v4.0 Bleeding (Hemorrhage) Grades:

0=None
1=Mild; intervention not indicated
2= Moderate symptoms; medical intervention or minor cauterization indicated
3= Transfusion, radiologic, endoscopic, or elective operative intervention indicated
4= Life-threatening consequences; urgent intervention indicated
[5=Death]

Criterion 4.2.5:

- Participants may be receiving fluconazole at the time of study enrollment.

Criterion 4.2.6:

- Contraindications include, but are not limited to: ongoing/active bleeding, very low platelet count, large brain metastases, etc.), or any condition that as judged by the treating physician would place the subject at increased risk of harm if s/he participated in the study. Weblinks to the FDA drug labels for the anticoagulation drugs used in this study can be found in the protocol.

5.0 SITE ACTIVATION

In order to open this study at your site, please complete the following steps:

- ☐ **Step 1:** Notify Alliance Foundation Trials (AFT) that your site is interested in opening the CANVAS Trial (AFT-28) by emailing **CANVAS@AllianceFoundationTrials.org**.
- ☐ **Step 2:** AFT will email you a Site Information Sheet (SIS) for you to complete.
- ☐ **Step 3:** Send the completed Site Information Sheet to **CANVAS@AllianceFoundationTrials.org**.
- ☐ **Step 4:** Once AFT receives your site's completed Site Information Sheet, AFT will send you a start-up package that will include information on the following:
  - ☐ Protocol and Protocol Signature page
  - ☐ ICF template (Model Informed Consent Form)
  - ☐ FDA Form 1572 template
  - ☐ REDCap user agreement
  - ☐ Information about how to:
    - ☐ You will receive an invitation from Wingspan to access the system. Log into and use your **Site Zone** account (This is the "electronic Trial Management File" application where you will upload and submit the required documents for site activation for this study. This is also where

you'll find the most up-to-date study documents, such as protocol, model informed consent form, tip sheets, etc.)

- ☐ Watch the **Virtual Protocol Training** (This is where study staff will watch the protocol training online video; no in-person SIV required by sponsor.)
- ☐ Log into and use your **REDCap** account (This is where you will enroll/randomize patients and enter all study data/case report forms.)

☐ **Step 5:** Obtain IRB Approval. This can be done in one of two ways:

- ☐ Option 1: Use the Alliance Foundation Trials (AFT) Central IRB as your site's IRB of record for this study [AFT will be using Quorum as the CIRB vendor for this study] **--OR--**
- ☐ Option 2: Submit this protocol to your site's institutional IRB
  - ☐ If you modify the required language found in the Model Informed Consent Form (Model ICF), you must submit a tracked-changes version of your local Informed Consent Form to **CANVAS@AllianceFoundationTrials.org** for review and approval **prior** to IRB submission.
  - ☐ If you do NOT modify the required language found in the Model Informed Consent Form (Model ICF), you still need to submit it to **CANVAS@AllianceFoundationTrials.org** for review and approval **prior** to IRB submission.
  - ☐ Please note: the Model Informed Consent Form (Model ICF) does not allow Legally Authorized Representatives to sign consent on behalf of a participant. In order to participate, a participant must be able to sign on his/her own behalf.
  - ☐ Please note: the Model Informed Consent Form (Model ICF) is now available in Spanish. Additional information for your site regarding the Spanish-language ICF:
    - Your site may use the Model ICF in Spanish; however, if your site requires additional translation of any language found in your local ICF, AFT is **not** able to provide your site with any additional funds to pay for the translation of your local ICF.
    - If your site has an established procedure whereby Spanish-language participants can be consented via the use of a Spanish-language short form plus an English-language long form plus involvement of an interpreter, then this method is acceptable. Any fees associated with the use of an interpreter will be at your

site's expense. Your site is not mandated to use the Spanish-language long-form ICF.

☐ **Step 6:** Complete the required study training:

To complete the required protocol training, each individual listed on the Delegation of Authority Log must:

☐ Watch the Protocol Training online video available here:

- The training for **study staff** can be found here (15-minute video): **https://vimeo.com/310853060/83ed78f342**
- The training for **physicians** can be found here (9-minute video): **https://vimeo.com/310855828/43624a2713**

☐ **Step 7:** Upload all of the following forms and documents into your Site Zone account:

☐ IRB approval memo

☐ IRB approved informed consent form

☐ Protocol Signature page signed by the Site PI

☐ Delegation of Authority log

☐ Completed and Signed FDA Form 1572 (from Site PI only; site sub-investigators who will be consenting and treating patients on this trial should be listed on the Site PI's FDA Form1572)

☐ Human subject research training for the PI

☐ The following are required for your site Principal Investigator

☐ CV (curriculum vitae) signed and dated within 3 years

☐ **Step 8:** Once all requirements above have been met, your site will receive a Site Activation Memo. Your site cannot consent and enroll patients into the CANVAS (AFT-28) study without this memo.

6.0 PATIENT ENROLLMENT AND RANDOMIZATION PROCEDURES

In order to enroll and randomize a participant, site staff should complete the following steps:

☐ Ensure all eligibility criteria have been met within the protocol stated timeframes (the Eligibility Checklist/Enrollment Form can be found here: https://redcap.partners.org/redcap/).

☐ Ensure patient has signed an appropriate informed consent form (ICF) and HIPAA authorization form. (At some sites, the ICF and HIPAA authorization are two separate documents each requiring participant signature. At other sites, the HIPAA authorization is contained within the ICF, so only the ICF requires participant signature).

Sites will enroll participants to this study using REDCap. To enroll a participant, follow these steps:

- ☐ Log into https://redcap.partners.org/redcap/.
  - ➢ If you have problem with or questions about REDCap, please contact the Central Study Coordinator at 617-632-4490 or **CANVAS_Coordinator@dfci.harvard.edu**.
- ☐ Click on the "My Projects" tab.
- ☐ Click the project link titled: "CANVAS Trial (AFT-28)."
- ☐ In the menu on the left-hand side of the screen, click on "Add / Edit Records".
- ☐ In the middle of the page, click on "Add new record".
- ☐ Fill out the Eligibility Checklist/Enrollment Form.
- ☐ Toward the end of the Eligibility Checklist/Enrollment Form, click the button that says "Randomize".
- ☐ Immediately after clicking "Randomize", a box will pop up that tells you to which arm the participant was randomized.
- ☐ Click "Save Record" at the bottom of the Eligibility Checklist/Enrollment Form.
- ☐ Immediately after saving the record, be sure to notify the participant's Treating Physician of:
  a) The participant's unique study ID number
  b) The study arm to which the participant has been randomized

** If you need expedited assistance during normal business hours (M-F, 8a-4p EST), please contact the Central Study Coordinator at 617-632-4490 or CANVAS_Coordinator@dfci.harvard.edu.

6.1 Stratification Factors and Treatment Assignments

6.1.1 Stratification Factors – None

6.1.2 Treatment Assignments

Participants will be randomized 1:1 to either

- **ARM 1 – Intervention Arm, DOAC** (choice of rivaroxaban, apixaban, edoxaban, or dabigatran)
- **ARM 2 – Usual Care Arm, LMWH/warfarin** (choice of LMWH with or without a transition to warfarin)

*If an eligible participant is offered randomization and **declines** randomization**, then a limited number of participants (up to N=190) will be allowed to enroll in the Preference Cohort. In this case, the treating physician and patient will choose protocol treatment on Arm 1 or Arm 2 (non-randomized).***

****The randomized cohort CLOSED to new enrollment in April, 2020. The preference cohort is CLOSED to new enrollment.**

See Treatment Plan/Intervention section for details regarding protocol treatment.

7.0 SCHEDULE OF ASSESSMENTS

Laboratory and clinical parameters during treatment **are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician**. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of cancer patients on this trial.

	Prior to Enrollment (≤ 7 days prior to enrollment)	**Baseline** (After participant signs informed consent but before protocol treatment begins)	**2-weeks after enrollment** (+/- 2 weeks)	**3-months after enrollment** (+/- 1 month)	**6-months after enrollment** (+/- 1 month)
Tests & Observations	-	Tests & observations are **not required** per protocol; conduct test & observations (e.g., history, physical, etc.) as needed to provide appropriate, standard care.			
Routine adverse event reporting	-	• Routine adverse event reporting is **not required** per protocol; conduct adverse event assessments as needed to provide appropriate, standard care.			
Expedited serious adverse event (SAE) reporting, see Adverse Events Section	-	**For this study, SAE requiring expedited reporting is defined as:** ALL adverse events that meet the following criteria MUST be reported via the Expedited SAE Reporting Form at https://redcap.partners.org: 1) All deaths on study require expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. 2) Any grade 3, 4, or 5 bleeding or hemorrhaging event. 3) Any AEs that result in blood transfusion(s). 4) Any thromboembolic event (e.g., VTE, DVT, PE, blood clot, thrombosis, or embolism). 5) Edema, dyspnea, stroke, and/or respiratory failure must be reported IF AND ONLY IF related to a thromboembolic event (e.g., VTE, DVT, PE, blood clot, thrombosis, or embolism). 6) All other events do NOT need to be reported as expedited SAEs.			
Laboratory Studies+	• Platelet count ≥50,000 per mm^3 • CrCl ≥ 15 ml/min as calculated by the Cockcroft-Gault method • Measure albumin (not an eligibility criteria, but should be recorded)	• Lab studies are **not required** per protocol; conduct lab studies as needed to provide appropriate, standard care (*e.g., if a participant receives warfarin, conduct routine blood monitoring per standard-of-care*). • Making note of the following types of lab studies in the participant's medical record is recommended but not required: hepatic, renal, platelet counts, CBC [complete blood count], red cell count, etc.			

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	Prior to Enrollment (≤ 7 days prior to enrollment)	**Baseline** (After participant signs informed consent but before protocol treatment begins)	**2-weeks after enrollment** (+/- 2 weeks)	**3-months after enrollment** (+/- 1 month)	**6-months after enrollment** (+/- 1 month)
Case Report Forms (CRFs) to be completed **by sites**	-	Eligibility Checklist/ Enrollment Form	Treatment Status Update Form	-	Medical Record Abstraction Form
CRFs to be completed **by sites OR by Central Study Coordinator**	-	Change in Enrollment Status/Off-Study Form (as needed)			
Participant Questionnaires (see patient-facing study materials)	-	Baseline Study Questionnaire administered by Enrolling Site	-	Follow-up Study Questionnaire administered by Central Study Coordinator	Follow-up Study Questionnaire administered by Central Study Coordinator
Patient Medication Diary^	-	REQUIRED: Participants will keep a monthly patient medication diary while on study. The patient medication diary can be printed directly from the protocol appendix and given to the participant (each participant should receive 6 copies of the diary, one for each month s/he is on study). The medication diary should be returned to the Central Study Coordinator each month.^			

[+] In this pragmatic trial, labs and clinical endpoints collected under routine clinical care will be used for eligibility and trial execution.

^ Because this is a pragmatic effectiveness trial whereby the protocol does not mandate monthly study visits, extra effort is needed to ensure we successfully collect medication diaries from participants. There are many ways a mediation diary can be collected:

- The **patient** can return the his/her monthly medication diary directly to the Central Study Coordinator each month. Depending on the patient's preference, each month s/he may:
    - **Email** a copy of (or picture of) their diary to CANVAS_Coordinator@dfci.harvard.edu
    - **Call** their diary into 617-632-4490
    - **Mail** their diary to CANVAS TRIAL, 450 Brookline Avenue, D-1014, Boston, MA 02215
    - **Fax** their diary to 617-394-2801, ATTENTION: CANVAS Coordinator
    - **Hand** their diary to a member of the study staff at your clinic; the staff member at your site can then send the diary to the CANVAS Coordinator via email, phone call, mail, or fax. You site may also upload this data directly into REDCap,
- Your **site** staff must proactively ask participants for their medication diaries following this procedure:
    - Contact participant up to three times for drug diaries via in person, phone, email, or postal mail.
    - If a participant gives you his/her drug diary, you can send it to the CANVAS Coordinator via email, phone call, mail, or fax.
    - If a drug diary is more than three months late after your site staff has made its three attempts to contact participants, then the **CANVAS Coordinator** may contact participants for their medication diaries up to three times via any of the following: email,

phone call, and/or mail. If the CANVAS Coordinator is unsuccessful at getting diaries from participants after three attempts, then the form will be considered missing.
Note: Your site staff are responsible for notifying the CANVAS Coordinator that you exhausted your attempts to contact the participant.

- Patients may report drug diary data orally to sites or central study coordinator, which can then be recorded by study staff on a paper diary which may then serve as source documentation.

Note about missing forms:

- If any of the following forms are missing for a participant, then this would constitute a major protocol violation:
  - Eligibility Checklist/Enrollment Form
  - Treatment Status Update Form
  - Medical Record Abstraction Form
  - Change in Enrollment Status/Off-Study Form (as needed)
  - Expedited Serious Adverse Event (SAE) Reporting Form (as/if needed)
- Protocol violations must be filed after a form is missing for greater than 30 days after the data entry window has closed (please refer to Section 7.0 for schedule of assessments).

- If any of the following forms are missing for a participant despite best efforts by Central Study Coordinator and Site Staff to collect from participant, then this does not constitute a major or minor protocol violation:
  - Baseline Study Questionnaire
  - Follow-up Study Questionnaire - 3 months
  - Follow-up Study Questionnaire - 6 months
  - Medication Diary - Month 1 of 6
  - Medication Diary - Month 2 of 6
  - Medication Diary - Month 3 of 6
  - Medication Diary - Month 4 of 6
  - Medication Diary - Month 5 of 6
  - Medication Diary - Month 6 of 6

Note about questionnaires and drug diaries:

- Study questionnaires and patient-reported drug diaries continue through the 6th month no matter how long the subject actually received protocol-directed anticoagulation.
- Site study staff should complete the Medical Record Abstraction Form at the end of the 6th month no matter how long the subject actually received protocol-directed anticoagulation.
- Because this is a pragmatic effectiveness trial whereby the protocol does not mandate regular study visits, drug accountability will be captured via the patient-reported drug diaries/questionnaires and the site's 6-month medical record abstraction.

8.0 STUDY PROCEDURES

This section describes the study procedures and data collection procedures for this study.

8.1 Screen, approach, and obtain informed consent

When a cancer patient is diagnosed with a VTE, s/he should be screened for eligibility. If the patient is determined to be eligible, then the site clinician should approach the patients within 30

days of the index VTE diagnosis, explain the study, and ask the patient if s/he would like to participate. Consent should be obtained by following Health and Human Services (HHS) guidelines (http://www.hhs.gov/ohrp/policy/consent/) as well as site-specific policies for obtaining informed consent for research. If the patient agrees to participate, the consenting physician and the patient will both sign the informed consent form. The original copy of the signed informed consent form should be kept in the participant's study file at the site, and a copy should be given to the participant for his/her records. Informed consent may be obtained in inpatient or outpatient care settings. Patients may be invited to participate by phone but in-person signed informed consent is a prerequisite to enrollment and randomization.

8.2 Eligibility Checklist/Enrollment Form

If the participant signs the informed consent document, the study staff at the site should fill out the Eligibility Checklist/Enrollment Form and submit it via REDCap (https://redcap.partners.org), as described in 9.2 Data Submission using REDCap.

8.3 Treatment Arm

Participants will be randomized 1:1 to either

- **ARM 1 – Intervention Arm, DOAC** (choice of rivaroxaban, apixaban, edoxaban, or dabigatran)
- **ARM 2 – Usual Care Arm, LMWH/warfarin** (choice of LMWH with or without a transition to warfarin)

*If an eligible participant is offered randomization and **declines** randomization, then a limited number of participants (up to N=190) will be allowed to enroll in the Preference Cohort. In this case, the treating physician and patient will choose protocol treatment on Arm 1 or Arm 2 (non-randomized).***

****The randomized cohort CLOSED to new enrollment in April, 2020. The preference cohort is CLOSED to new enrollment.**

See Treatment Plan/Intervention section for details regarding protocol treatment.

For ALL study participants (regardless of treatment arm or cohort), the study procedures described in this section of this protocol are applicable and identical.

8.4 Baseline Study Questionnaire

The **Baseline Study Questionnaire** will collect: patient-reported ECOG performance status, SF-12 HR-QOL (the Optum SF-12 Health Survey uses 12 questions to measure functional health and well-being from the patient's point of view), information about the index VTE, cancer type/status, co-morbidities, influence of insurance coverage on decision to be participate, and demographics.

It is the enrolling site staff's responsibility to administer the Baseline Study Questionnaire to the participant.

Timing: The Baseline Study Questionnaire must be administered after the participant has signed informed consent but before protocol treatment begins.

> **NOTE:** The Baseline Study Questionnaire can be administered before or after the participant has been enrolled/ randomized as long as it is administered after the

participant has signed informed consent and before protocol treatment begins. It is operationally easiest to administer the Baseline Study Questionnaire immediately after the participant signs informed consent.

To administer the questionnaire:

- ☐ Print the questionnaire directly from Appendix: Baseline Study Questionnaire – for administration via paper
- ☐ Have the participant fill out the paper questionnaire
- ☐ Enter the participant's responses into REDCap (https://redcap.partners.org)
- ☐ Keep the original questionnaire in the participant's study file at your site

It is acceptable for a surrogate to complete the questionnaire on behalf of the patient. The surrogate can be a friend, family member, caregiver, or other appropriate person. The surrogate is NOT a research participant and should complete the questionnaire *on behalf of the patient*. No information about the surrogate will be collected.

If for any reason, the enrolling site staff is unable to administer the Baseline Study Questionnaire, they must notify the Central Study Coordinator immediately so that the Central Study Coordinator may attempt to administer the Baseline Study Questionnaire via phone, secure weblink, or postal mail. The Central Study Coordinator can be reached at: 617-632-4490 and/or CANVAS_Coordinator@dfci.harvard.edu.

See 9.2 Data Submission using REDCap for instructions on how to enter and submit the data via REDCap.

8.5 Treatment Status Update Form

2-weeks after the participant has been enrolled, the site staff should submit the Treatment Status Update Form via https://redcap.partners.org. The Treatment Status Update Form will ask sites to report: (1) whether or not the participant is receiving treatment in accordance with the treatment arm to which s/he was assigned (see next paragraph for more information); (2) if yes, which anticoagulation drug is the participant receiving; (3) if no, why not (e.g., due to insurance non-coverage, patient refusal, transfer of care, receive no anticoagulation therapy, other); (4) if no, which anticoagulation drug is the participant receiving, if any.

If participant is not receiving treatment in accordance with the treatment arm to which s/he was assigned, that is NOT a protocol violation. Please keep this patient ON STUDY.

- Arm 1: Switching between DOACs is allowed
- Arm 2: Switching between LMWH/warfarin is allowed
- Anticoagulation "breaks" and "gaps" are not protocol violations
- Arm 1: Switching to LMWH is discouraged but is not a protocol violation.
- Arm 2: Switching to DOAC is discouraged but is not a protocol violation
- Record abstraction and medication diaries will ascertain these rates

8.6 Follow-up Study Questionnaires

The **Follow-up Study Questionnaire** (administered at 3-months post-enrollment and again at 6-months post enrollment) will collect: patient-reported ECOG performance status, SF-12 HR-QOL, anticoagulation therapy information including dose and adherence, ACTS anticoagulation

therapy burden (the Anti-Clot Treatment Scale (ACTS) is a 15-item patient-reported instrument of satisfaction with anticoagulant treatment), VTE recurrence, and bleeding.

It is the **Central Study Coordinator's responsibility** to administer the Follow-up Study Questionnaires to the participant.

Timing: The Follow-up Study Questionnaire will be administered once at 3-months (+/- 1 month) after enrollment and once at 6-months (+/- 1 month) after enrollment.

- If a participant has withdrawn consent to participate in the patient questionnaire component of this study, then do not administer any additional Follow-up Study Questionnaires.

The **Central Study Coordinator** will contact the participant via phone, internet, and/or postal mail depending on participant preferences.

- To administer the questionnaire via SECURE WEBLINK: The Central Study Coordinator will email the secure, individualized questionnaire link to the participant. The participant will enter his/her responses directly into REDCap using the link provided.
- To administer the questionnaire via PHONE: The Central Study Coordinator will follow the phone script found in Appendix: Follow-up Study Questionnaire – for administration via phone". The Central Study Coordinator will enter the participant's responses into REDCap.
- To administer the questionnaire via POSTAL MAIL: The Central Study Coordinator will print and mail the paper version of the Follow-up Study Questionnaire along with a prepaid return envelope to the participant's mailing address. The Central Study Coordinator will enter the participant's responses into REDCap, and keep the original paper copy in the participant's central study file.

It is acceptable for a surrogate to complete the questionnaire on behalf of the patient. The surrogate can be a friend, family member, caregiver, or other appropriate person. The surrogate is NOT a research participant and should complete the questionnaire *on behalf of the patient*. No information about the surrogate will be collected. Each Follow-up Study Questionnaire may be completed by the patient himself/herself, by the same surrogate who completed a previous questionnaire on the participant's behalf, or by a different surrogate. The questionnaire will elicit whether the patient completed responses directly or via a surrogate.

A participant will be contacted by the Central Study Coordinator up to 4 times in an attempt to complete each Follow-up Study Questionnaire. If a participant has not responded after 4 attempts, then the Central Study Coordinator will ask the enrolling site's staff to attempt contact. If the enrolling site's staff is unable to make contact after 4 attempts, then the questionnaire will be marked as missing, and the participant will not be contacted regarding that questionnaire again.

Instructions to site:
If the Central Study Coordinator is unable to contact an enrolled participant being treated at your site, the Central Study Coordinator will notify you by phone and email and ask for your assistance in contacting the participant. If the participant has an upcoming clinic visit, the Central Study Coordinator may ask you to administer the Follow-up Study Questionnaire in-person. Your assistance is greatly appreciated!

After the participant/surrogate completes each Follow-up Study Questionnaire, the Central Study Coordinator will email or mail him/her (depending on the respondent's preferences) a $25.00 Amazon.com gift card.

8.7 Medical Record Abstraction

At six months after enrollment (or at the time of the participant's death, whichever occurs first), the site will conduct and submit the Medical Record Abstraction Form via REDCap. The information needed to fill out the Medical Record Abstraction Form can be found in the participant's medical record.

The Medical Record Abstraction Form will collect the following types of information:

- Demographics (age at diagnosis, current age, gender, race, ethnicity, marital status)
- Clinician-reported ECOG performance status
- Height, weight, BMI (body mass index)
- Tobacco history (current use/former use/never use and pack year history)
- Comorbidities using the Katz scale
- VTE type, location, presentation, history
- Tumor site, histology, and metastatic sites of disease
- Presence of brain metastases
- Lab Values (hepatic, renal, platelet counts, CBC [complete blood count], red cell count)
- Other treatment types (hormone, chemo, surgery, radiation)
- Bleeding, recurrent VTE, survival
- Anticoagulation therapy selection, doses, modifications
- Medication history during time on study.

8.8 Change in Enrollment Status/Off-Study Form

Whenever there is a change in a participant's enrollment status, the Change in Enrollment Status/Off-Study Form should be completed and submitted via REDCap (https://redcap.partners.org) within 1 week of the change. A Change in Enrollment Status/Off-Study Form can be submitted by the site or by the Central Study Coordinator.

Reasons a participant might have a change in enrollment status or go off-study include:

1. STUDY COMPLETE: Participant is being taken off study because s/he has reached the end of the 6-month study period.
2. ACTIVE PARTICIPANT WITHDRAWAL: Study participant actively withdrew consent for one or more components of the study, including:
    a. protocol treatment, and/or
    b. participant questionnaires, and/or
    c. participant medication diaries, and/or
    d. access to his/her medical record for Medical Record Abstraction.

    HOW TO PROCEED: Unless the participant explicitly (and preferably in writing) withdraws consent to access his/her medical record, site study staff SHOULD complete the Medical Record Abstraction Form 6-months after the participant was enrolled.
3. CLINICIAN WITHDRAWAL: Clinician took participant off protocol treatment. Please note that after taking a subject off protocol treatment, study questionnaires and patient-

reported drug diaries continue through the 6th month. Site study staff should complete the Medical Record Abstraction Form at the end of the 6th month no matter how long the subject actually received protocol-directed anticoagulation.

4. LOST TO FOLLOW-UP: Study participant is lost to follow-up. The site staff should still complete the Medical Record Abstraction Form 6-months after the participant was enrolled.
5. DEATH: If a study participant dies, the site staff should complete the Medical Record Abstraction Form, then complete a change of enrollment/off-study form in REDCap If the central study coordinator is informed of a participant's death in real time during a touch for a Follow-Up Study Questionnaire, a surrogate may complete the survey. Surrogates may not be contacted directly for Follow-Up Study Questionnaires.
6. FOUND TO BE INELIGIBILE: Participant was enrolled on the trial but was later found to be ineligible. Select one:
    a. Yes, protocol treatment will continue [treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment].
    b. No, protocol treatment will not continue [in this case, study questionnaires and patient-reported drug diaries continue through the 6th month. Site study staff should complete the Medical Record Abstraction Form at the end of the 6th month no matter how long the subject actually received protocol-directed anticoagulation].
7. OTHER: Please specify.

8.9 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. Notification of the local IRB and/or Central IRB may be necessary per local/central IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) should still complete all follow-up requirements: the Medical Record Abstraction (done by the site) and the 3 participant study questionnaires (at baseline, 3-months, and 6-months) and the patient-reported drug diaries. Data will be analyzed using the intention to treat cohortin sensitivity analyses

8.10 Notice regarding proprietary content embedded in the patient questionnaires

Two validated, proprietary instruments are embedded in the patient questionnaires for this study:

1. **SF-12** - The Optum™ SF-12v2® Health Survey uses 12 questions to measure functional health and well-being from the patient's point of view. The SF-12 shall be and remain at all times the property of Optum.

2. **ACTS** - The Anti-Clot Treatment Scale (ACTS) is a 15-item patient-reported instrument of satisfaction with anticoagulant treatment. It includes a 12-item ACTS Burdens scale and a 3-item ACTS Benefits scale. The ACTS shall be and remain at all times the property of Bayer Pharma AG, as licensed by Mapi Research Trust.[32]

a. ACTS Author: Stefan Cano and Donaa Lamping with a research grant provided by Bayer Pharma AG
b. ACTS Owner: Bayer Pharma AG
c. ACTS Copyright notice: ACTS © Bayer AG, 2006. All Rights Reserved.
d. ACTS References: [32] The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in venous thromboembolism patients. Heath Qual Life Outcomes. 2012 Sep 26; 10:120.

AFT-approved and activated sites may use and administer the Survey Materials at their site, only on behalf of AFT, only during the Study term, and only for the Approved Purpose (as outlined in this protocol). Sites may not use the Survey Materials for any other purpose, including but not limited to reproducing, copying, modifying, or distributing the licensed survey content without the owner's consent. See Appendix for more information.

9.0 DATA COLLECTION AND SUBMISSION

9.1 Summary of data collection and submission:

	Data collected <u>from site</u>		Data collected <u>from participant</u>	
Timing	**Case Report Form (CRF)**	**How to collect & submit data**	**Name of Assessment**	**How to collect & submit data**
At time of enrollment (<u>after</u> patient signs informed consent but <u>before</u> protocol treatment begins)	Eligibility Checklist/ Enrollment Form	➢Submit electronically via REDCap, detailed instructions in section 9.2	Baseline Study Questionnaire	➢Administered by enrolling site staff ➢Filled out by the participant and/or their surrogate ➢Responses entered into REDCap by site staff
2-weeks post enrollment	Treatment Status Update Form	➢Submit electronically via REDCap	-	-
3-months post enrollment	-	-	Follow-up Study Questionnaire	➢Administered by the Central Study Coordinator ➢Filled out by the participant and/or their surrogate (respondent given $25 gift card upon completion) ➢Responses entered into REDCap by Central Study Coordinator
6-months post enrollment	Medical Record Abstraction Form	➢ Medical record abstraction (i.e., chart review) conducted by site staff ➢Entered into REDCap by site staff	Follow-up Study Questionnaire	➢Administered by the Central Study Coordinator ➢Filled out by the participant and/or their surrogate (respondent given $25 gift card upon completion) ➢Responses entered into REDCap by Central Study Coordinator
Ongoing, as needed (from enrollment through off-study)	Expedited Adverse Event Reporting Change in Enrollment Status/Off-Study Form	➢Entered into REDCap by site staff when a reportable event occurs, see section 12 for details ➢Entered into REDCap by site staff or Central Study Coordinator whenever a change in participant status occurs, see section 8.8 for details	-	-

9.2 Data Submission using REDCap

Sites will use REDCap to: (a) enroll and randomize participants, (b) submit case report forms (CRFs), and (c) conduct Expedited Adverse Event Reporting for this study.

To enroll and randomized participants via REDCap, see the instructions found in **Section 6.0**.

To enter and submit **case report forms** and to conduct Expedited **Adverse Event Reporting** via REDCap, follow these steps:

- ☐ Log into https://redcap.partners.org.
  - ➢ If you have problem with or questions about REDCap, please contact the Central Study Coordinator at 617-632-4490 or CANVAS_Coordinator@dfci.harvard.edu.
- ☐ Click on the "My Projects" tab.
- ☐ Click the project link titled: "AFT-28: CANVAS Trial."
- ☐ In the menu on the left-hand side of the screen, click on "Add / Edit Records"
- ☐ From the dropdown menu, select the Study ID Number for the participant of interest.
- ☐ In the menu on the left-hand side of the screen, click on the name of the CRF you would like to edit.
- ☐ When done entering data, scroll down and click "Save Record" at the bottom of the form.

10.0 DRUG INFORMATION

10.1 General Considerations

All drugs used in this study are commercially available, FDA-approved, and are being prescribed on-label. This study does **not** involve any investigational new drugs/agents/devices (no INDs).

This study will NOT provide any drugs because all drugs used in this study are commercially available, FDA-approved, and are being prescribed on-label. Drugs should be prescribed per standard practice at your site and billed to the patient's insurance company or the patient as your sites does for any other standard medication.

If a patient is assigned to a treatment and unable to receive that treatment as a result of insurance coverage issues, this should be recorded.

10.2 Drug Information

FDA Package Inserts:

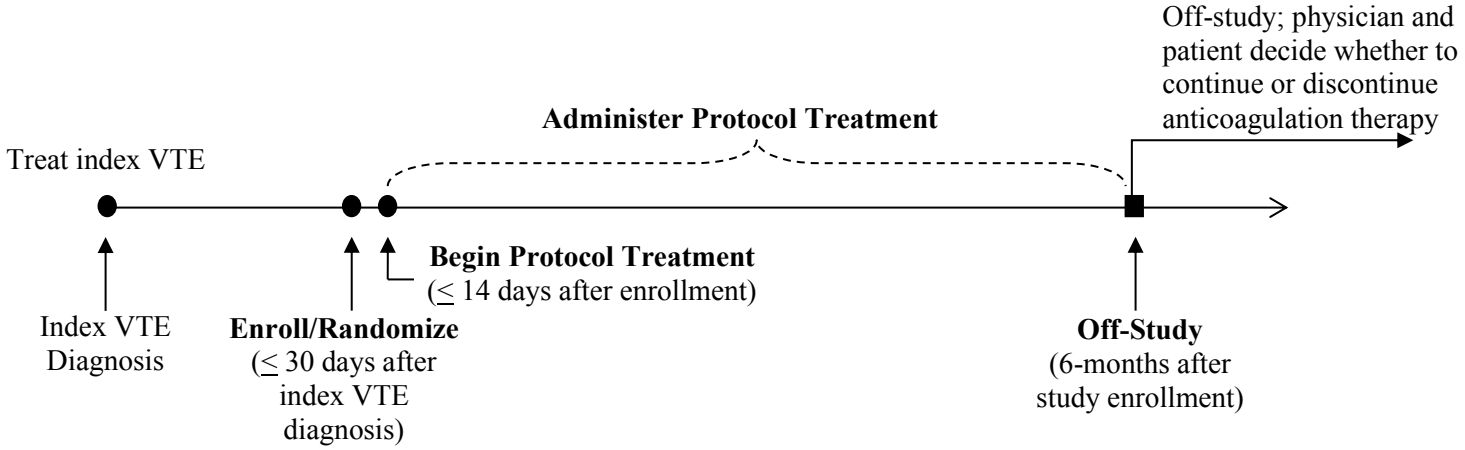
Generic name	Brand name	Drug class	Link to FDA Package Insert^ • *How supplied & storage*: Section 16 of package insert • *Administration*: Section 2 • *Drug interactions*: Section 7 • *Pharmacokinetics*: Section 12.3 • *Adverse reactions*: Section 6
ARM 1 – Intervention Arm, DOAC			
Rivaroxaban	Xarelto®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022406s023lbl.pdf
Apixaban	Eliquis®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202155s020lbl.pdf
Edoxaban	Savaysa®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206316s012lbl.pdf
Dabigatran	Pradaxa®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022512s035lbl.pdf
ARM 2 – Usual Care Arm, LMWH/warfarin			
Dalteparin	Fragmin®	LMWH	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020287s069lbl.pdf
Enoxaparin	Lovenox®	LMWH	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020164s110lbl.pdf
Fondaparinux	Arixtra®	Indirect Xa inhibitor	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021345s035lbl.pdf
Warfarin	Coumadin®	Vitamin K antagonist	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009218s118lbl.pdf

^Links to FDA Package Inserts are included here for easy reference; however, if the FDA Package Insert/Safety Labeling changes, you are required to use the most up-to-date FDA Package Insert/Safety Label.

11.0 TREATMENT PLAN/INTERVENTION

Regardless of protocol treatment arm and/or anticoagulation drug(s) used, treat the patient according to individual institutional guidelines, the best clinical judgment of the responsible physician, and in consultation with national treatment guidelines and the drug's package insert.

11.1 Overview of treatment plan



1. Diagnosis of index VTE
2. Treat index VTE (any anticoagulation drug/strategy may be used to treat the index VTE; this is not part of the study)
3. **Study enrollment and randomization (must occur within 30 days of the index VTE diagnosis).**
4. Switch from therapy to treat the index VTE (not part of study) to anticoagulation therapy intended to prevent recurrent VTE (i.e., protocol treatment). **Begin protocol treatment ≤ 14 days after enrollment.**
   - If participant consented to randomization, treat according to the arm to which the participant was randomized, either: Randomized Arm 1 or Randomized Arm 2.
   - If participant did not consent to randomization, treat according to the arm that the participant and his/her treating physician chose, either: Non-Randomized Arm 1 or Non-Randomized Arm 2**

     ****The randomized cohort CLOSED to new enrollment in April, 2020. The preference cohort is CLOSED to new enrollment.**
5. Six months after the participant is enrolled, protocol treatment ends; **After protocol treatment period ends, continue or discontinue anticoagulation therapy according to individual institutional guidelines and the best clinical judgment of the responsible physician. Record the decision.**

11.2 Protocol Treatment

Protocol treatment should commence ≤ 14 days after date of enrollment.

Protocol Treatment Arms:

Participants will be randomized 1:1 to either

- **ARM 1 – Intervention Arm, DOAC** (choice of rivaroxaban, apixaban, edoxaban, or dabigatran)
- **ARM 2 – Usual Care Arm, LMWH/warfarin** (choice of LMWH with or without a transition to warfarin)

*If an eligible participant is offered randomization and **declines** randomization, then a limited number of participants (up to N=190) will be allowed to enroll in the Preference Cohort. In this case, the treating physician and patient will choose protocol treatment on Arm 1 or Arm 2 (non-randomized).***

****The randomized cohort CLOSED to new enrollment in April, 2020. The preference cohort is CLOSED to new enrollment.**

10.2.1 ARM 1 – Intervention Arm, DOAC

For all participants in **ARM 1 – Intervention Arm, DOAC**, the treating physician and participant should choose anticoagulation therapy with Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (Savaysa), or Dabigatran (Pradaxa).

10.2.2 ARM 2 – Usual Care Arm, LMWH/warfarin:

For all participants in **ARM 2 – Usual Care Arm, LMWH/warfarin**, the treating physician and participant should choose anticoagulation therapy with Warfarin (Coumadin); Dalteparin (Fragmin); Enoxaparin (Lovenox); or Fondaparinux (Arixtra).

11.3 Selecting an Anticoagulant

11.3.1 Practice Guidelines

When selecting an appropriate anticoagulant for the participant, please refer to standard practice guidelines, some of which are provided here for easy reference:

- **National Comprehensive Cancer Network (NCCN) Guidelines: Cancer-Associated Venous Thromboembolic Disease**[15]
  Available at: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf

- **American College of Chest Physicians Evidence-Based Clinical Practice Guidelines** [16]
  Available at:
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278055/pdf/112295.pdf

- **European Society for Medical Oncology Clinical Practice Guidelines** [17]

  Available at:
  http://annonc.oxfordjournals.org/content/22/suppl_6/vi85.full.pdf+html

- **American Thoracic Society (ATS) - Statements, Guidelines & Reports**
  Available at: https://www.thoracic.org/statements/

- **The American Society of Hematology (ASH) - ASH Clinical Practice Guidelines**
  Available at: http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx

- **American Society of Clinical Oncology (ASCO) Guidelines, Tools, & Resources** [33]
  Available at: https://www.asco.org/practice-guidelines/quality-guidelines/guidelines

  [33]Available at: http://jco.ascopubs.org/content/33/6/654.full.pdf+html

- **Up to Date™** and **ClinicalKey™** are for-profit content developers to which many clinicians subscribe.

11.3.2 FDA Package Inserts

When selecting an appropriate anticoagulant for the participant, please also refer to the drug(s) FDA Package Inserts, provided here for easy reference:

Generic name	Brand name	Drug class	Link to FDA Package Insert^ • *How supplied & storage*: Section 16 of package insert • *Administration*: Section 2 • *Drug interactions*: Section 7 • *Pharmacokinetics*: Section 12.3 • *Adverse reactions*: Section 6
ARM 1 – Intervention Arm, DOAC			
Rivaroxaban	Xarelto®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022406s023lbl.pdf
Apixaban	Eliquis®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202155s020lbl.pdf
Edoxaban	Savaysa®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206316s012lbl.pdf
Dabigatran	Pradaxa®	DOAC	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022512s035lbl.pdf
ARM 2 – Usual Care Arm, LMWH/warfarin			
Dalteparin	Fragmin®	LMWH	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020287s069lbl.pdf
Enoxaparin	Lovenox®	LMWH	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020164s110lbl.pdf
Fondaparinux	Arixtra®	Indirect Xa inhibitor	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021345s035lbl.pdf
Warfarin	Coumadin®	Vitamin K antagonist	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009218s118lbl.pdf

^Links to FDA Package Inserts are included here for easy reference; however, if the FDA Package Insert/Safety Labeling changes, you are required to use the most up-to-date FDA Package Insert/Safety Label.

11.4 Protocol treatment administration - Dosing

For complete dosing information, please review the FDA package inserts. The dosing information (pulled directly from the FDA package inserts) for each of the LMWH, warfarin, or DOAC drugs is provided here for quick reference. Review recommendations for converting to or from other oral or parenteral anticoagulants. Temporarily discontinue before invasive or surgical procedures when possible, then restart when feasible. Interruptions in anticoagulation do NOT constitute protocol violations. Treatment actually administered and breaks in treatment should be recorded on the Medical Record Abstraction Form. Monitoring for patients on anticoagulation therapy should be as per local management protocols. Patients on warfarin receiving chemotherapy should have their INR checked once per week. Patients with stable INR not receiving chemotherapy may have their INR checked every other week. All patients irrespective of anticoagulation strategy should be instructed to call their physicians with new bleeding or evidence of recurrent VTE.

Dosing Summary Table

Drug	**Dosing Summary^** *(for complete dosing information, please review standard practice guidelines and FDA package insert)*
ARM 1 – Intervention Arm, DOAC	
Rivaroxaban	Treatment of DVT: • Initial treatment of VTE is 15 mg bid x 21 days. If patient has completed 21 days of other anticoagulant treatment then use 20 mg qd. If treatment with other anticoagulant has started, use rivaroxaban at 15 mg bid to complete 21 days then transition to 20 mg qd. • Orally, take 15 mg and 20 mg tablets with food; take 10 mg tablets with or without food. • Avoid if creatinine clearance (CrCl) ≤ 30 mL/min • Dose modify or avoid in hepatic failure • If a dose is not taken at the scheduled time, administer the dose as soon as possible on the same day.
Apixaban	• Initial treatment of VTE dose is 10 mg bid x 7 days, then transition to 5 mg bid. If patient has completed 7 days of treatment with another anticoagulant, then use 5 mg bid; otherwise, use 10 mg bid to complete 7 days of anticoagulant treatment before switching to 5 mg bid. • In patients with at least 2 of the following characteristics: age >=80 years, body weight <=60 kg, or serum creatinine >=1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. [For patients who require a decreased dose of Apixaban the *suggested* dosing is seven days of 5 mg bid followed by 2.5 mg bid for duration of treatment.] • Dose modify or avoid in hepatic failure • If a dose is not taken at the scheduled time, the dose should be taken as soon as possible on the same day [the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose] and twice daily administration should be resumed. The dose should not be doubled to make up for a missed dose.
Edoxaban	Treatment of DVT and PE: • Requires 5 days of treatment with a parenteral agent before initiating edoxaban for VTE treatment • The recommended dose is 60 mg once daily • The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors • No dose modification for hepatic failure • If a dose is missed, the dose should be taken as soon as possible on the same day. Dosing should resume the next day according to the normal dosing schedule. The dose should not be doubled to make up for a missed dose.

Table continued from the previous page

Drug	Dosing Summary^ *(for complete dosing information, please review the FDA package insert)*
Dabigatran	• Requires 5 days of treatment with a parenteral agent before initiating dabiagtran for VTE treatment • For patients with CrCl >30 mL/min: 150 mg orally, twice daily • For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily • No dose modification for hepatic failure • Instruct patients not to chew, break, or open capsules • If a dose is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. The missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose should not be doubled to make up for a missed dose.
ARM 2 – Usual Care Arm, LMWH/warfarin	
Dalteparin	Treatment of VTE in patients with cancer: • Month 1: 200 IU/kg subcutaneous once daily • Months 2 - 6: 150 IU/kg subcutaneous once daily • For missed doses: patients should inject the missed dose as soon as they remember. However, if it is almost time* for the next dose, skip the missed dose and continue regular dosing schedule. Patients should not inject a double dose to make up for a missed one.
Enoxaparin	Treatment of DVT: • 1 mg/kg sc bid (preferred) • Alternative dosing 1.5 mg/kg sc qd is acceptable • For missed doses: patients should inject the missed dose as soon as they remember. However, if it is almost time* for the next dose, skip the missed dose and continue regular dosing schedule. Patients should not inject a double dose to make up for a missed one.
Fondaparinux	Treatment of deep vein thrombosis (DVT): • Weight < 50 kg 5 mg sc qd • Weight 50-100kg 7.5 mg sc qd • Weight > 100 kg 10 mg sc qd • For missed doses: if participants miss a dose, they should take their dose as soon as they remember. They should not take 2 doses at the same time.
Warfarin	• Individualize dosing regimen for each patient, and adjust based on INR response. • Review conversion instructions from other anticoagulants. • The anticoagulant effect of warfarin persists beyond 24 hours. If a patient misses a dose of warfarin at the intended time of day, the patient should take the dose as soon as possible on the same day. The patient should not double the dose the next day to make up for a missed dose.

sc = subcutaneous; qd = daily; bid = twice daily

^The CANVAS protocol does not mandate doses so clinicians should prescribe a dose that they feel is in the best interest of the patient. Dose modifications are not protocol violations. Study chair Jean Connors is available to discuss individual patient level dosing if needed.

**Regarding "almost time for the next dose:" The package inserts/full prescribing information does not provide any more detail on this issue. Decisions regarding "almost time for the next dose" are at the treating clinician's discretion. In general:*

- ***If a patient is prescribed an injection once per day, then:*** *if a patient misses a dose at the intended time of day, they should take the dose as soon as possible on the same day. The patient should not double the dose the next day to make up for the missed dose.*
- ***If a patient is prescribed an injection twice per day (i.e., once every 12-hours), then:*** *if a patient misses a dose at the intended time of day, the patient should take the dose as soon as possible unless his/her next schedule dose time is in ≤6 hours. If his/her next scheduled dose time is in ≤6 hours, then skip the missed dose and resume with the next scheduled dose.*

11.4.1 Additional dosing considerations – ARM 1 - Intervention Arm, DOAC:

The DOACs have different initial dosing strategies that should be understood. Dosing is based on the time after diagnosis of the index VTE. All patients should be treated with full intensity at time of index VTE diagnosis unless significant contraindications exist.

- **Dabigatran and edoxaban:** at least 5 days of a parenteral agent which can be any of the LMWH agents or intravenous heparin are required for initial treatment followed by a switch to dabigatran or edoxaban.
- **Rivaroxaban:** the dose of 15 mg BID is used for the first 21 days after VTE diagnosis, followed by change in dose to 20 mg once daily. If participants have had 21 days or more of LMWH therapy prior to enrollment/initiation they may initiate rivaroxaban at the 20 mg qd dose. If participants have had fewer than 21 days of LMWH at initiation they should receive treatment at the initial (acute dose) to complete 21 days total before switching to 20 mg qd.
- **Apixaban:** 10 mg bid is used for the first week of treatment after VTE diagnosis followed by 5 mg BID. If participants have had 7 days of LMWH therapy prior to randomization they may initiate apixaban at the 5mg bid dose, if treatment has not been for 7 days then use 10 mg bid to complete 7 days before switching to 5 mg bid.

sc = subcutaneous; qd = daily; bid = twice daily

Decisions regarding vomited doses are at the treating clinician's discretion. In general, if a patient **can see the undigested pill in their vomit,** then the vomited dose can be treated like a missed dose. If the patient vomits more than 1 hour after taking the dose, then the dose should not be made up.

Table: Renal Insufficiency Dose: Initial and Chronic Treatment of VTE
The table details initial dosing and chronic dosing suggestions in the setting of normal and abnormal renal function. Please refer to package inserts and local guidelines for details. Deviations and rounding do **not** constitute protocol violations.

ARM 1 – Intervention Arm, DOAC				
CrCl mL/min	**Rivaroxaban**	**Apixaban**	**Edoxaban***	**Dabigatran***
Normal Renal Function > 50	Initial: 15 mg bid x 3 weeks Chronic: 3 week, 20 mg qd	Initial: 10 mg bid x 1 week Chronic: 5 mg bid	Initial: LMWH x 5 days Chronic: 60 mg qd	Initial: LMWH x 5 days Chronic: 150 mg bid
30-49	Initial: 15 mg bid x 3 weeks Chronic: 20 mg qd	Initial: 10 mg bid x 1 week Chronic: 5 mg bid	Initial: LMWH x 5 days Chronic: 30 mg qd	Initial: LMWH x 5 days Chronic: 150 mg bid
< 30	Avoid	Initial: 10 mg bid x 1 week Chronic: 5 mg bid	Initial: LMWH x 5 days Chronic: 30 mg qd	Initial: LMWH x 5 days Chronic: 75 mg bid
< 15	Avoid	Initial:10 mg bid x 1 week Chronic: 5 mg bid	Not recommended	Initial: LMWH x 5 days Chronic: 75mg bid

sc = subcutaneous; qd = daily; bid = twice daily
***Edoxaban and Dabigatran require initial treatment with parenteral agent for 5 days.**

11.4.2 Additional dosing considerations – ARM 2 – Usual Care Arm, LMWH/warfarin:

- Individualize warfarin dosing regimen for each patient, and adjust based on INR response.
- Monitoring: per local warfarin management protocols but no less frequently than every 2 weeks
- Review conversion instructions from other anticoagulants.
- Rounding is acceptable in accordance with pre-filled syringes/vial sizes
- Switching between LMWHs is acceptable
- Switching between LMWH and warfarin is acceptable

11.5 Dose Modifications

Dose modifications <u>are allowed</u>, and are not considered protocol violations.

- Skipped or omitted doses are not protocol violations.
- Drug discontinuation is not a protocol violation.
- Delayed or postponed doses are not protocol violations.
- Dose reductions are not protocol violations and should be done at the discretion of the treating clinician.
- Re-escalation of doses is not a protocol violation and should be done at the discretion of the treating clinician.

When making dose modifications, the guiding principal should be: Regardless of treatment arm and/or anticoagulation drug(s) used, treat the patient according to individual institutional guidelines, the best clinical judgment of the responsible physician, and in consultation with the drug's package insert and with national treatment guidelines.

At 3 and 6 months, participants will report their use of treatment, the number of days with no anticoagulant therapy, and the number of days with each type of anticoagulant therapy. Study CRAs will also abstract this information from medical records at 6 months.

11.6 Ancillary therapy, concomitant medications, and supportive care

Use of ancillary/concomitant therapy <u>is allowed</u> and should be done according to individual institutional guidelines, and the best clinical judgment of the responsible physician. Supportive care measures are allowed during trial participation (i.e., antiemetics, antidiarrheals, steroids, others). Supportive care should be administered at the discretion of the treating clinician. Use of ancillary/concomitant therapy is not a protocol violation. Use of aspirin and NSAIDS is also at the discretion of the treating physician based on risk/benefits.

Patients should receive all supportive and usual standard care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. When administering anticoagulation therapy, ancillary therapy, concomitant medications, and/or supportive care, **<u>the treating clinician(s) must take into account drug interactions as per standard good clinical practice.</u>** For complete drug interaction information, please review the FDA package inserts. The drug interaction information for each of the LMWH, warfarin, or DOAC drugs (pulled directly from the FDA package inserts) is provided here for quick reference.

Drug Interactions Summary Table - Excerpted from FDA Package Inserts

Drug	Drug Interactions Summary *(for complete drug interaction information, please review the FDA package insert)*
ARM 1 – Intervention Arm, DOAC	
Rivaroxaban	• Combined P-gp and strong CYP3A4 inhibitors and inducers: Avoid concomitant use • Prophylaxis of DVT: Anticoagulants: Avoid concomitant use
Apixaban	• Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban: Reduce apixaban dose to 2.5 mg or avoid concomitant use. • Simultaneous use of strong inducers of CYP3A4 and P-gp reduces blood levels of apixaban: Avoid concomitant use.
Edoxaban	• Anticoagulants: Avoid concomitant use • Rifampin: Avoid concomitant use
Dabigatran	• P-gp inducers rifampin: Avoid coadministration with dabigatran • P-gp inhibitors dronedarone and systemic ketoconazole in patients with moderate renal impairment (CrCl 30-50 mL/min): Consider reducing dabigatran dose to 75 mg twice daily • P-gp inhibitors in patients with severe renal impairment (CrCl <30 mL/min): dabigatran use not recommended
ARM 2 – Usual Care Arm, LMWH/warfarin	
Dalteparin	• Use Dalteparin with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents
Enoxaparin	• Discontinue agents which may enhance hemorrhage risk prior to initiation of enoxaparin or conduct close clinical and laboratory monitoring
Fondaparinux	• Discontinue agents that may enhance the risk of hemorrhage prior to initiation of therapy with Fondaparinux unless essential. If co-administration is necessary, monitor patients closely for hemorrhage.
Warfarin	• Consult labeling of all concurrently used drugs for complete information about interactions with warfarin or increased risks for bleeding. • Inhibitors and inducers of CYP2C9, 1A2, or 3A4: May alter warfarin exposure. Monitor INR closely when any such drug is used with warfarin. • Drugs that increase bleeding risk: Closely monitor patients receiving any such drug (e.g., other anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory drugs, serotonin reuptake inhibitors). • Antibiotics and antifungals: Closely monitor INR when initiating or stopping an antibiotic or antifungal course of therapy. • Botanical (herbal) products: Some may influence patient response to warfarin necessitating close INR monitoring.

11.7 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on study forms.
- Follow the patient for protocol endpoints.

12.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research. For this trial, adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms using the codes provided.

12.1 Overview

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

- For this trial, routine "Solicited Adverse Event" reporting is **not** required.
- For this trial, "Expedited Serious Adverse Event" reporting **is required** using the SAE Report Form in REDCap (https://redcap.partners.org). Adverse event reporting begins at enrollment should continue until 30 days after the last administration of on-study protocol treatment.

12.2 Routine adverse event reporting

Because this study only involves on-label use of FDA-approved drugs, **no routine "Solicited Adverse Event" reporting is required**. Even though routine solicited adverse event reporting is not required for this trial, treat the patient according to individual institutional guidelines, the best clinical judgment of the responsible physician, and in consultation with the drug's package insert and standard practice guidelines.

On the Medical Record Abstraction Form which will be completed at 6-months post enrollment (or at the time of the participant's death, whichever occurs first), the following will be ascertained via retrospective chart review:

- Information about bleeding events that occurred during the 6-month study period.
- Information about recurrent VTEs that occurred during the 6-month study period.
- Information about any other adverse reactions during the 6-month study period.

12.3 Expedited Adverse Event Reporting (AFT-28)

Investigators are required to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is located at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All events determined to be "reportable" in an expedited manner must be reported using REDCap (https://redcap.partners.org). NOTE: CTEP-AERS is **not** being used for this trial.

Investigators should also report all events determined to be "reportable" in an expedited manner to their local IRB per institutional policy.

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

For this study, SAE requiring expedited reporting is defined as:

ALL adverse events that meet the following criteria MUST be reported via the Expedited SAE Reporting Form at https://redcap.partners.org:

1) All deaths on study require expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.
2) Any grade 3, 4, or 5 bleeding or hemorrhaging event.
3) Any AEs that result in blood transfusion(s).
4) Any thromboembolic event (e.g., VTE, DVT, PE, blood clot, thrombosis, or embolism).
5) Edema, dyspnea, stroke, and/or respiratory failure must be reported IF AND ONLY IF related to a thromboembolic event (e.g., VTE, DVT, PE, blood clot, thrombosis, or embolism).
6) All other events do NOT need to be reported as expedited SAEs.

If an AE meets the definition of SAE requiring expeditated reporting as defined above, the AE must initially be reported via the Expedited SAE Reporting Form at https://redcap.partners.org ≤ 24 hours of learning of the AE, followed by a complete expedited report via the Expedited SAE Reporting Form at https://redcap.partners.org ≤ 5 calendar days of the initial 24-hour report.

Serious adverse events that occur more than 30 days after the last administration of study protocol treatment and have an attribution of possible, probable, or definite require reporting as follows:

- If an AE meets the definition of SAE requiring expeditated reporting as defined above, the AE must initially be reported via the Expedited SAE Reporting Form at https://redcap.partners.org ≤ 24 hours of learning of the AE, followed by a complete expedited report via the Expedited SAE Reporting Form at https://redcap.partners.org ≤ 5 calendar days of the initial 24-hour report.

Treatment expected adverse events include those listed in Section 12.4 Expected Adverse Reactions and in the package insert.

12.4 Expected Adverse Reactions

For complete adverse reaction information, please review the FDA package inserts. The adverse reaction information for each of the LMWH, warfarin, or DOAC drugs (pulled directly from the FDA package inserts) is provided here for quick reference.

Expected Adverse Reaction Summary Table

Drug	**Expected Adverse Reaction Summary** *(for complete adverse reaction information, please review the FDA package insert)*
ARM 1 – Intervention Arm, DOAC	
Rivaroxaban	The most common adverse reaction (>5%) was **bleeding**.
Apixaban	Most common adverse reactions (>1%) are related to **bleeding**.
Edoxaban	Treatment of DVT and PE: The most common adverse reactions (≥ 1%) are **bleeding**, **rash**, **abnormal liver function tests** and **anemia**.

Dabigatran	Most common adverse reactions (>15%) are **gastritis-like symptoms** and **bleeding**
ARM 2 – Usual Care Arm, LMWH/warfarin	
Dalteparin	Most common adverse reaction is **hematoma** at the injection site.
Enoxaparin	Most common adverse reactions (>1%) were **bleeding**, **anemia**, **thrombocytopenia**, **elevation of serum aminotransferase**, **diarrhea**, and **nausea**.
Fondaparinux	The most common adverse reactions are **bleeding** complications. **Mild local irritation** (injection site bleeding, rash, and pruritus) may occur following subcutaneous injection. **Anemia**, **insomnia**, **increased wound drainage**, **hypokalemia**, **dizziness**, **hypotension**, **confusion**, **bullous eruption**, **hematoma**, **post-operative hemorrhage**, and **purpura** may occur.
Warfarin	Most common adverse reactions are **fatal and nonfatal hemorrhage** from any tissue or organ.

12.5 FDA MedWatch

MedWatch is the FDA's Safety Information and Adverse Event Reporting Program. MedWatch is the FDA gateway for clinically important safety information and reporting serious problems with human medical products.

MedWatch reporting is not required per protocol; however, if you would like to report SUSPECTED ADVERSE REACTIONS, you may contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch at your discretion.

12.6 New or Recurrent VTEs on Study

If a patient experiences a new or recurrent VTE while on study, sites should follow these steps:

- First and foremost, please make anticoagulation treatment decisions that are in the best interest of the patient. Sites are **NOT** required to stick with the anticoagulant to which the patient was assigned per protocol. Sites can switch anti-clot drugs (to an anti-clot drug from Arm 1, Arm 2, or neither arm), dose modify drugs, or discontinue drugs. **Select the strategy** that is best for the patient in view of the totality of their care.
    - **For patients on treatment with a DOAC:** From a standard of care approach, if your patient was assigned to treatment with a DOAC and they develop a new VTE while taking the DOAC without interruption, it is recommended that they switch to a parenteral agent/standard of care.
    - **For patients taking warfarin:** If the patient is on warfarin, we suggest that they switch to a parenteral agent. If the patient develops a new VTE while taking full dose parenteral agent without interruption then we suggest escalating the dose to 125% as is convention based on small study results[34, 35]

- If the participant is taken off protocol treatment, please:
    - have a member of your study staff (CRA) log into REDCap and fill out a "**Change in Enrollment Status/Off-Study Form**."
        - On the form, please select the 3rd response option which says:

"CLINICIAN WITHDRAWAL: Clinician took participant off protocol treatment. Please note that after taking a subject off protocol treatment, study questionnaires and patient-reported drug diaries continue through the 6th month. Site study staff should complete the Medical Record Abstraction Form at the end of the 6th month no matter how long the subject actually received protocol-directed anticoagulation."

- There are no study questionnaires or medical record tracking that extend beyond 6 months.

13.0 STATISTICAL CONSIDERATIONS

Note: This revised statistical considerations section reflects the result of monthly data monitoring for April, 2020. As of April 28th, 2020, the study has enrolled a total of 808 patients. Please note, 140 patients were enrolled to the preference cohort which closed in December 2017. The remaining patients are enrolled in the randomized cohort. ***Please see the finalized Statistical Analysis Plan (SAP) outlined in Appendix 18.0. Select references from this plan are included below.***

Study Design: Randomized Effectiveness Trial with Hybrid observational component
Sample Size: ***The planned total sample size is revised from 890 to 808 total patients (140 patients in the preference cohort and 668 in the randomized cohort) due to significant curtailment of the accrual rate caused by the COVID-19 pandemic. The study closed to new enrollment in April 2020. Anticipated final N is expected to be 811 patients.***
Accrual Time: Approximately 3 years
Study Duration: Approximately 3.5 years

Primary Endpoint:
Cumulative VTE recurrence reported by patients or their clinicians at 6 months

Secondary Endpoints:
- Cumulative incidence of major bleeding reported by patients or clinicians at 6 months
- Cumulative incidence of all bleeding events and bleeding according to its severity in the following categories:1) major bleeding, 2) clinically significant non-major and 3) nuisance
- Cumulative incidence of death at 6 months
- Overall HRQOL at 3 and 6 months
- Overall score on the Anti-Clot Therapy Scale at 3 and 6 months

Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting): anticipated **November 2020**

13.1 Summary of the study design and rationale

The study design is a **randomized effectiveness study** to evaluate the effectiveness of DOAC therapy compared to usual care with LMWH/warfarin. Participants who decline randomization will be offered the opportunity to participate in the preference cohort**. This is a hybrid design that consists of both a randomized cohort and a preference cohort. Eligible patients who accept randomization will be enrolled in the study (**the randomized cohort**), and they will be randomly assigned either the DOAC therapy group or the usual care group. Those patients who decline randomization but choose treatment on one of the two study arms will be invited to the study (**the preference cohort****). The rationale of employing the hybrid study design with the two cohorts is that both cohorts have own strength, and they complement each other. Specifically, the randomized controlled design is the most rigorous study design for comparing treatment alternatives. However, it may not capture the effectiveness under the real-world setting because the analysis population is limited to only those patients who accept randomization. On the other hand, the non-randomized study (i.e., the preference cohort**) assesses effectiveness more likely under real-world circumstances, while the internal validity (i.e., the comparability between the two treatment groups) has to rely on unverifiable assumptions. **This hybrid study design will maximize the totality of evidence of comparative effectiveness between the DOAC and usual care.** All statistical analyses (details below) will be performed with the randomized cohort and the preference cohort separately, and they will be combined using a meta-analytic methodology

(details below). The results from the randomized cohort will be considered as the primary results.

****Based on the results of monthly data monitoring conducted in June 2017, the preference cohort is CLOSED to new enrollment, following the closing rule #2 specified in the protocol. The randomized cohort CLOSED to new enrollment in April, 2020.**

13.2 Accrual

13.2.1 Total accrual

The accrual rate is expected to be approximately **30 patients per month**. Patients who accept randomization will be randomized equally to the two arms (randomized cohort). Patient who decline randomization but choose either of the two arms will be invited to enroll (preference cohort**). Since preliminary clinical experience suggests that the majority of patients will accept randomization, we expect that 80% of the 30 patients (i.e., 24 patients per month) will accept randomization and the rest of the 20% (6 patients per month) will decline. Because the results of monthly data monitoring conducted in June 2017 met a criterion for closing the accrual to the preference cohort (see 13.2.2), it was closed after 140 patients were enrolled to it. **Approximately 810 patients** (670 patients in the randomized cohort and 140 patients in the preference cohort) will be enrolled in the study. We planned to enroll a **total of 890 patients** (750 patients in the randomized cohort and 140 patients in the preference cohort) with 32 months of accrual period, considering that the accrual rate in the first few months of the study is generally slower than thereafter. However, due to significant curtailment of the accrual rate caused by the COVID-19 pandemic since March 2020, we have revised the planned total sample size to 810 patients. (see 13.2.4 for details)

****The randomized cohort CLOSED to new enrollment in April, 2020. The preference cohort is CLOSED to new enrollment.**

13.2.2 Monitoring of accrual and the stopping rule

Note: The conditions for "Preference Cohort Closing Rule #2" below have been met as of June 1st, 2017; the pre-set imbalance between arm selection in the preference cohort has been met. As such, the preference cohort is CLOSED to new enrollment. **This section was intentionally left as it was, in order to clarify the closing rules specified in the original protocol.**

Although we expect that 80% of eligible patients will accept randomization, the true proportion is not known. In addition, there is no reliable information about which arm will be more likely chosen among the patients in the preference cohort. If almost all patients chose one of the two arms, the preference cohort would not provide reliable information regarding the treatment difference. Therefore, to avoid such a potential imbalance, we will continuously monitor the number of enrolled patients in each cohort and each arm. Following the rules below, we will terminate the enrollment of the preference cohort.

Preference Cohort Closing Rule #1:
All statistical analyses (details below) will be performed with the randomized cohort and the preference cohort separately, and they will be combined using a meta-analytic

methodology (details below). The results from the randomized cohort will be considered the primary results. Therefore, to guarantee the statistical power for the analysis with the randomized cohort, we will cap the number of patients in a preference cohort to be 190. **Once 190 patients are enrolled in the preference cohort**, we will close the accrual to the preference cohort, keeping the enrollment of the randomized cohort open.

Preference Cohort Closing Rule #2:**
The rule #2 is set to avoid an extreme imbalance of the number of patients between the two arms in the preference cohort. The ideal situation in terms of statistical efficiency for the analysis is that the number of patients who choose the DOAC arm is the same as those choose the usual care arm (i.e., 50% vs. 50%), and deviation from this balance induces information loss for the analyses. Thus, we will close the accrual of the preference cohort if we observe a large imbalance in sample size between two groups, even if the number of the preference cohort has not reached the cap of the 190. Specifically, we require that, out of the 190 patients, at least 38 patients (i.e., 20% of 190) should be in each of the two arms. After 50 patients are enrolled in the preference cohort, we will continuously calculate the conditional probability that sample size of either arm in the preference cohort will end up to be less than 38. When this conditional probability becomes great than 50%, we will consider terminating the enrollment to the preference cohort. The stopping boundary corresponding to this rule is given in following Table.

****The randomized cohort CLOSED to new enrollment in April, 2020. The conditions for "Preference Cohort Closing Rule #2" have been met; the pre-set imbalance between arm selection in the preference cohort has been met. As such, the preference cohort is CLOSED to new enrollment.**

Table: Closing rule #2

Total number of patients enrolled in the preference cohort	Stopping boundary	
	Observed sample size in the preference cohort	Observed absolute difference in sample size between groups
50	10 vs. 40	30 or larger
60	12 vs. 48	36 or larger
70	14 vs. 56	42 or larger
80	16 vs. 64	48 or larger
90	18 vs. 72	54 or larger
100	20 vs. 80	60 or larger
110	22 vs. 88	66 or larger
120	24 vs. 96	72 or larger
130	26 vs. 104	78 or larger
140	28 vs. 112	84 or larger
150	30 vs. 120	90 or larger

13.2.3 Planned modifications of accrual to enrich enrollment for pre-specified subgroup analyses

We plan to evaluate effectiveness in the following three key subgroups of cancer patients.

Patients with:

1) Highly Thrombogenic Tumors
2) Indwelling Central Venous Catheters
3) Thrombocytopenia

The accrual goals for the three subgroups are 300, 500 and 200 patients, respectively (see below for sample size and power considerations about these subgroups). We anticipate that each of the accrual goals will be automatically achieved by enrolling a total of 810 patients in this study. However, it may not be the case. Therefore, as soon as the 700th patient is enrolled in the study, we will project the total number of patients that will be enrolled in each of the three subgroups. If enrollment is not on track for any of the three subgroups, we will consider modifying the eligibility criteria, so that the accrual goals of those subgroups can be achieved. In that case, the modified eligibility criteria will be active right after the 700th patient is enrolled.

13.2.4 Modifications to the size of the final analytic cohort; Updated statistical proposal (Prepared by Hajime Uno PhD, Study Statistician in April 2020):

As of April 28, 2020, the study has enrolled at total of 808 patients. Of the 808, 668 were enrolled in the randomized cohort. When we discontinue the patient enrollment now, the total sample size is expected to be around 810 depending on the exact date of formal closure. With this sample size, the power of non-inferiority test already reaches 90% (See Table). For superiority, it is slightly below the 80% target power at 75%. The expected length of confidence interval (CI) for the difference in event rate is now 6.1% with 808 patients, and it would have been 5.8% with the planned total sample size (N=890). This suggests that the gain in the precision may be marginal. Given the challenges to continued accrual in the setting of the COVID-19 pandemic and the recently reported results of the Caravaggio study we propose revision as follows.

Table: Power calculation for the primary analysis

Date	N (Randomized Cohort)	N (total)	Length of CI for difference	Power	
				Non-inferiority	Superiority
Revised Statistical Analysis Plan	**668**	**808**	**6.1%**	**0.900**	**0.756**
Originally Planned Goal	**750**	**890**	**5.8%**	**0.927**	**0.797**

Enrollment to the CANVAS trial will therefore be suspended in April 2020 before reaching the original proposed 890 patient accrual mark. The final N will be reported upon study closure at all sites but it is expected to be around 810 depending on the exact date of formal closure

13.3 Statistical Considerations for Primary Endpoint – *Please see Appendix 18.0 for more details in the SAP.*

13.3.1 Primary Analysis

The primary aim of this study is to compare the intervention and comparator arms with respect to their ability to prevent recurrent VTE. Because the intervention (DOAC therapy) is more easily administered than the comparator (usual care with LMWH warfarin), DOAC is expected to have higher adherence and therefore decreased incidence of VTE. Accordingly, a noninferiority design with a superiority alternative is preferred, as

described by Friedlen et al[36]. The primary analysis will test the noninferiority of the DOAC therapy with the primary analytic cohort (modified ITT population of the randomized cohort). If noninferiority is demonstrated, superiority of the DOAC therapy will be tested.

Because VTE is often a proximate cause of death in cancer patients' unexplained sudden demise, but diagnostic procedures are rarely performed (post-mortem scans, autopsies, etc.), we considered VTEs that were clinically significant as the primary outcome on the basis of an antemortem diagnosis. Separately, we looked at all-cause deaths because deaths from cancer and deaths from VTE are difficult and in many cases nearly impossible to distinguish. This is the approach that has been taken in efficacy trials that have compared DOAC and LMWH therapies. We will estimate the cumulative incidence of recurrent VTE at 6 months using the standard competing risk analysis method,[49] where death will be treated as a competing risk. We calculate the difference in the 6 month incidence rate between groups and corresponding 0.90 confidence interval (CI).

1) Non-inferiority test of DOAC

The hypothesis for testing the noninferiority of the DOAC strategy is that the difference in the primary endpoint at 6 months is no greater than a noninferiority margin of 3% for the intervention-comparator. This noninferiority margin was selected based on what is acceptable to patients based on patient-stakeholder input as well as on input provided by clinicians

To confirm the noninferiority hypothesis, we will construct a two-sided 90% confidence interval (CI) for the difference in the cumulative incidence of the primary endpoint at 6 months (180 days). If the upper bound of the CI is less than 3%, we will conclude that the DOAC management strategy is non-inferior to the LMWH/warfarin strategy for management of VTE in patients with cancer.

2) Superiority test of DOAC

If noninferiority of DOAC is demonstrated, a superiority test of DOAC will be performed using a one-sided 0.05 significance level and the same two-sided 90% CI for the difference in the event rate of the primary endpoint at 6 months as used for the noninferiority test. When the upper bound of the CI is less than 0, we will conclude that DOAC therapy is superior to LMWH/warfarin in terms of VTE prevention. Because we will perform the superiority test only after the noninferiority of DOAC is demonstrated, the overall type I error rate is maintained at the 0.05 level (one-sided) without splitting alpha.[36]

13.3.2 Interim Analysis

This study design incorporates several interim analyses and one final analysis for the comparison of the primary endpoint. A 90% two-sided repeated confidence interval (RCI)[37] for the difference in the cumulative incidence rate of VTE at 6 months (DOAC minus Usual Care) between two arms was estimated. We use the critical values based on the Lan-DeMets error spending function[38] corresponding to the truncated version of O'Brien-Fleming boundaries.[39]

Prior to the final analysis, four interim analyses were conducted on September 7, 2018, March 22, 2019, September 9, 2019, and March 25, 2020. Given these interim analyses, the critical value for the final analysis will be 1.710, which corresponds to a one-sided 0.0436 alpha. The confidence coefficient of the 90% two-sided RCI will be 91.28% for the final analysis.

13.3.3 Secondary Analyses

1) Analysis with other summary measures

The absolute difference in 6-month event rate based on the cumulative incidence function (CIF) is the primary summary measure of the between-group difference. As a secondary analysis, we will calculate subhazard ratio using a Fine and Gray model[40]. We will construct 0.90 CIs for these measures.

2) Alternative way to handle deaths

In the primary analysis, we handle deaths as competing risks and estimate the recurrent VTE rates by the CIF approach. As a secondary analysis, we will handle deaths as censored observations and estimate the recurrent VTE event rates by the Kaplan-Meier method. We will calculate the hazard ratio and difference in the event rate at 6 months and corresponding 0.90 CIs.

3) Sensitivity Analyses including data from the preference cohort

This study allowed a limited number of participants to enroll in the preference cohort if an eligible participant declines randomization. The Preference Cohort Closing Rules were pre-specified in Section 13.2.2 in the study protocol to specify the maximum number of participants enrolled in the preference cohort and to avoid an extreme imbalance of the number of participants between two groups. The results of monthly data monitoring in June 2017 observed the pre-set imbalance criteria in between arm selection. The enrollment to the preference cohort was therefore closed in December 2017, after 140 patients had enrolled in it.

First, we will compare characteristics between the preference and randomized cohorts to assess potential heterogeneity between the two cohorts. Fisher's exact test will be used for nominal categorical variables, and two-sample Wilcoxon tests will be used for ordered categorical or continuous variables.

We will estimate the difference in VTE event rate at 6 months and its standard error from the preference cohort, using a propensity score approach to adjust for potential treatment selection.[41] We will then combine the result with that from the randomized cohort, using a weighted average. An optimal weight (i.e., the reciprocals of the variance) will be used. The resulting estimate for the difference in VTE event rate and 90% CI can be considered an overall average treatment effect of DOAC across the full cohort. In no circumstance will analyses of the full cohort be presented as primary.

4) Analysis by type of VTE recurrence

We will also conduct the same analyses for each of the following subtypes of VTE recurrence.

1) Pulmonary embolism (PE) with or without deep vein thrombosis (DVT)
2) DVT without PE

5) Adjusted analyses

We will perform adjusted analysis to estimate the adjusted treatment effect, using generalized linear mixed-effects models with the logit link. Censored observations will be handled by the inverse probability censoring weight technique.[42] The participating sites will be included as random-effects.[43] Those baseline characteristics variables (see 3.4) whose distributions are not balanced between two groups ($p<0.05$) in the randomization cohort will be included as fixed-effects in the models for adjustment.

6) Sensitivity Analyses using the ITT and the per protocol populations.

Sensitivity analyses will be performed with alternative cohort specification. We will repeat all the analyses using the ITT population and then using the per-protocol population.

13.3 Statistical Considerations for Secondary Endpoints

13.3.4 Secondary endpoints

- Cumulative incidence of major bleeding reported by either patients or clinicians at 6 months
- Cumulative incidence of all bleeding events and bleeding according to its severity in the following categories:1) major bleeding, 2) clinically significant non-major and 3) nuisance
- Cumulative incidence of death at 6 months
- Overall HRQOL at 3 and 6 months
- Overall score on the Anti-Clot Therapy Scale at 3 and 6 months

13.3.5 Analyses for secondary endpoints

1) Cumulative rates of major bleeding reported by patients or clinicians at 6 months (NCI CTCAE Grade 3, 4, or 5)

We will repeat the analogous analyses as performed for the primary endpoint (see 13.3.1). The primary analysis plan for major bleeding, fatal or non-fatal, is also based on the sequential evaluation of noninferiority and superiority. We will construct a two-sided 90% CI for the difference in the cumulative incidence rate for the composite outcomes of major bleeding and death. If the upper bound of the CI is less than 2.5%, we will conclude that DOAC is noninferior to LMWH/warfarin in terms of major bleeding. The same secondary analyses as planned for the primary endpoint will be performed. In contrast to clotting, fatal bleeding events are usually clinically manifest and recorded and therefore can be distinguished.

2) Cumulative incidence of all bleeding events reported by patients or clinicians at 6 months in the following categories: 1) major bleeding (Grade >=3), 2) clinically significant non-major (Grade 2); and,3) nuisance bleeding (Grade 1)

Clinically significant non-major bleeding is defined as Grade 2 Nuisance bleeding is defined as Grade 1 according to the NCI CTCAE criteria. We will perform the same analysis as described above for major bleeding events.

3) Mortality (Cumulative incidence of death at 6 months)

Time from randomization to death from any cause is a secondary endpoint. The study is powered to confirm the primary hypothesis for recurrent VTE; we do not anticipate enough power to perform a confirmatory analysis for all-cause mortality. We will instead focus on providing quantitative information for the between-group difference for this endpoint. We will describe the survival time distribution by treatment group using the Kaplan-Meier method. Also, we will compare the restricted mean survival times (RMST)[44] between groups. The truncation time point for calculating the RMST will be 6 months, which will give us an estimate of 6-month lifetime expectancy for each group. We will estimate the difference in RMST and corresponding 90% CI. Hazard ratio and its 90% CI will also be calculated if the proportional hazards assumption is reasonable. The determination of the violation of the proportional hazards assumption will be based on a significant p-value (<0.05) for the Grambsch and Therneau test. [45]

4) The Patient-Centered Experience of Anticoagulation QOL and Burdens

a. Health Related Quality of Life (SF-12) at 3 and 6 months

For SF-12, the primary analysis variable is the difference in the SF-12 mean change score from baseline. We will consider 2-point differences as clinically meaningful. We will use multiple imputations to handle missing observations.[46]

First, we will create 10 complete datasets, imputing missing values using chained equations, where we include measurements at baseline, 3 months, and 6 months. Second, we will estimate mean changes and the standard errors for each of the 10 complete sets. We will then use Rubin's method to derive an estimate for the difference in the mean change score between two groups. Using the resulting estimate and the standard error, we will perform a Z-test to evaluate equality of SF-12 scores between groups.

b. Anti-Clot Treatment Scale (ACTS) score at 3 and 6 months

For ACTS score, the primary analysis variables are the ACTS Burdens total score and the ACTS Benefits total score. We will consider 2-point differences as clinically meaningful. To minimize potential bias due to missing observations, we will allow and include surrogate estimates for all 3 patient-reported outcome assessments. Next, we will use multiple imputation to handle missing observations. First, we will create 10 complete datasets, imputing missing values using chained equations, where we include measurements at baseline, 3 months, and 6 months. Second, we will estimate mean changes and the standard errors for each of the 10 complete sets. Lastly, we will integrate the results using Rubin's method.

13.3.6 Other/Persistence with treatment Endpoints

- Performance status

  We will use the two-sample Wilcoxon test to evaluate between-group differences in ECOG PS.
- Cumulative rates of remaining on any anti-coagulation therapy at 3 and 6 months
- Cumulative rates of remaining on the assigned (and/or selected in the case of the preference cohort) anti-coagulation therapy at 3 and 6 months.

13.3.7 Safety endpoint evaluation

Safety endpoints:

- Major bleeding (primary protocol safety endpoint)
- Clinically significant non-major bleeding
- Any bleeding (major bleeding and clinically significant non-major bleeding and nuisance bleeding)
- Other Serious Adverse Events (SAE)

For this trial, "Expedited Serious Adverse Event" reporting is required using the SAE Report Form in REDCap. Adverse event reporting begins at enrollment and should continue until 30 days after the last administration of on-study protocol treatment. SAEs for other adverse events are reported via the following guidelines:

- Grade 1 or 2 adverse events that resulted in hospitalization for 24 or more hours, or
- Grade 3, 4, or 5 adverse events regardless of hospitalization

The analysis plan for major bleeding and any bleeding are outlined in section 13.3.5. Incidence of all other SAEs will be summarized by cohort, arm, grade, and type of SAE. Fisher's exact test will be performed to compare the event rates.

13.5 Heterogeneity of Treatment Effects

13.5.1 Subgroup Analysis

We will perform subgroup analyses to investigate the potential heterogeneity of treatment effects. For each subgroup, we will perform the same analyses described in the previous sections. The treatment effect by subgroup will be summarized by point estimates and corresponding 90% confidence intervals. We will create forest plots to display those results. This analysis will be performed with an exploratory purpose; we will not adjust for multiple comparisons.

First, we will focus on the 3 key subgroups described below because these groups are common, and decision making in these contexts is challenging for oncologists and patients. These 3 subgroups represent populations of particular interest for clinical decision makers.

13.5.1.1 Pre-specified subgroup 1: Patients with Highly Thrombogenic Tumors
We anticipate that at least 300 patients with lung (NSCLC and small cell), pancreas, esophagogastric and ovarian cancers are represented in the study sample. These patients have an even higher risk of VTE than cancer patients in

general. Based on anticipated higher adherence rates to DOAC therapy and the likelihood of warfarin failures in the LMWH/warfarin arm, we anticipate a slight advantage for DOACs over the standard care arm. As planned for the full cohort analysis, we will only test for superiority in the subgroup if noninferiority is met.

13.5.1.2. Pre-specified subgroup 2: Indwelling Central Venous Catheters
We anticipate that a subgroup of approximately 500 study participants will have an indwelling central venous catheter in place at the time of enrollment. This recruitment should not be challenging given how commonplace use of these catheters has become in routine oncology practice. The rate of VTEs is expected to be slightly higher for patients with a central venous catheter due to the excess risk of upper extremity clots.

13.5.1.3. Pre-specified subgroup 3: Thrombocytopenia
We will consider the subgroup of participants with baseline platelet counts less than 150,000/microliter. Thrombocytopenic cancer patients face high risk of VTE but also face higher risks of bleeding. In this setting, the choice of anticoagulation strategy is challenging.

13.5.1.4. Other preplanned subgroups
We will perform the same analysis for the following subgroups with an exploratory purpose.

- Sex (Male, Female)
- Age (below 65, equal or greater than 65)
- Participants with central nervous system (CNS) tumor involvement
- Participants with liver metastases
- Participants with albumin <3.5mg/dL
- Participants treated with bevacizumab
- Participants incidentally detected VTE on routine imaging studies (versus symptomatically detected VTE)
- Participants with metastatic disease (versus completely resected disease or no radiographic evidence of tumor)
- Participants with >80% days of persistence with anticoagulant therapy (vs. >50-80% vs. <=50%) by participant estimate
- Participants with >80% days of persistence with anticoagulant therapy (vs. >50-80% vs. <=50%) by medical record abstraction/dose refills
- Solid tumors versus hematologic malignancies

We will perform subgroup analyses to investigate the potential heterogeneity of treatment effects. For each subgroup, we will perform the same analysis described in the previous sections. The treatment effect by subgroup will be summarized by point estimates and corresponding 90% confidence intervals. We will create forest plots to display those results. This analysis will be performed with an exploratory purpose; we will not adjust for multiple comparisons.

13.6 Toxicity

Using the AFT mechanism, we will monitor reportable adverse events every month during the study. Every month, the study chair and the study statistician will determine if further review by the study team and the DMSB is necessary.

In particular, we will monitor the adverse event rates of 1) thrombosis, 2) bleeding and 3) all-cause of mortality. If a statistically significant difference in any of these adverse events is observed at any time during the study, the DMSB will consider recommending the termination or modification of the study from safety perspective.

Toxicity event rates will be compared between DOAC and LMWH/warfarin, using Fisher's exact test. Please see section 13.5 for evaluation of bleeding risk and categorization of bleeding events.

13.7 Other statistical considerations

Regarding missing values, we will perform both complete case analyses and multiple imputation analyses to account for missing data.[47]

13.8. Software

The statistical analyses will be performed with R version 4.0.2, Stata version 16, and SAS version 9.4.

13.8 Gender and Ethnicity

Based on preliminary clinical experience, the anticipated accrual in subgroups defined by gender and race is:

Category	Gender		Total
	Females	Males	
Ethnic Category[a]			
Hispanic or Latino	69	69	138
Not Hispanic or Latino	335	335	670
Ethnic Category: Total of all subjects	**404**	**404**	**808**
Racial Category[b]			
American Indian or Alaskan Native	5	5	10
Asian	22	22	44
Black or African American	53	53	106
Native Hawaiian or other Pacific Islander	1	1	2
White	313	313	626
Two or More Races	10	10	20
Racial Category: Total of all subjects	**404**	**404**	**808**

[a]Hispanic or Latino (17%), Not Hispanic or Latino (83%)
[b]American Indian or Alaskan Native (1.2%), Asian (5.4%), African-American (13.2%), Native Hawaiian or other Pacific Islander (0.2%), White (77.4%), Two or more races (2.5%)
Source: https://www.census.gov/quickfacts/table/PST045215/00

13.9 Study Monitoring

The study will be monitored by the AFT data safety and monitoring board (DSMB) to ensure objectivity and the safety of participants. The DSMB will meet twice each year either at a face-to-face meeting or by teleconference. At each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DMSB will also review formal interim analyses of the outcome data. If necessary, the DSMB will recommend study closure or modifications. Any DMSB recommendations for changes to the study will be circulated to investigators in the form of addenda to this protocol document. This study will adhere to standards for the conduct and reporting of RCTs described in the CONSORT statement.[48]

13.10 Endpoint Adjudication

All case report forms for patients with recurrent VTE and major bleeding episodes will be reviewed and categorized by physician adjudicators who are not knowledgeable of the patients' treatment assignment. Discrepant interpretations between any two endpoint adjudicators will be evaluated by a third adjudicator who is also not knowledgeable as to the patients' treatment assignments. Cases of discrepant interpretation of the primary endpoint will be discussed among the adjudicators until consensus is achieved.

13.11 Site Audits

Audits visits will be conducted on-site as part of the AFT investigator site audit program, according AFT policies and procedures. Not all patients will be audited. A minimum of 1 patient or at least 10% of PCORI-funded AFT trial cases at the site will be audited.

14.0 BUDGET

14.1 Funding

This trial is supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-1503-29805).

14.2 Site and per case reimbursement

Sites that open the CANVAS Trial (AFT-28) will receive the following site reimbursement rates:

$2,000 one-time seed funds payable upon submission of site IRB approval of the study

+$250 per case reimbursement payable upon submission of each Eligibility Checklist/Enrollment Form

+$500 per case reimbursement payable upon submission of each Medical Record Abstraction Form (1 Medical Record Abstraction Form required per participant, usually completed and submitted 6-months post enrollment)

Sites do not need to invoice AFT. Payments will be sent automatically based on data entered into REDCap.

14.3 Drug costs

This study will not provide any drugs because all drugs used in this study are FDA-approved and are being prescribed on-label. Drugs should be billed to the patient's insurance company or the patient as your site does for any other standard medication.

One practical aspect about the design of this study is that patients can be enrolled up to 30 days after the index VTE, and during that first 30 days, patient may be treated with any type of anticoagulant. This should give practitioners enough time to obtain prior authorizations for necessary insurance coverage, etc. During this period, participants can be started on LWMH and then transitioned to a DOAC when coverage has been obtained.

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16.0 Appendix: Notice regarding proprietary content embedded in the study questionnaires

NOTICE TO INVESTIGATIONAL SITES - APPENDIX C

Effective Date:	04/01/16
License:	QM034574
Licensee Name:	Alliance Foundation Trials, LLC
Study Term:	Beginning on 04/01/16 and ending on 09/30/19
Licensed Surveys:	SF-12v2 Standard Recall
Approved Purpose:	Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)

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Disclaimer. Optum makes no warranties to Site regarding the Licensed Surveys, and disclaims all implied warranties, including the warranties of merchantability and fitness for a specific purpose.

17.0 PATIENT-FACING STUDY MATERIALS

Not enclosed with this protocol.

To obtain copies of the following materials, either:

- Download them from SiteZone (https://sitezone.mywingspan.com/sitezone/#/trials), or
- Email CANVAS@AllianceFoundationTrials.org to request copies.

- Model Informed Consent Form – ENGLISH
- Model Informed Consent Form – SPANISH
- Baseline Questionnaire (available in 6 formats; content identical in all 6 formats)
  - Baseline Study Questionnaire – for administration via paper - ENGLISH
  - Baseline Study Questionnaire – for administration via secure weblink - ENGLISH
  - Baseline Study Questionnaire – for administration via phone - ENGLISH
  - Baseline Study Questionnaire – for administration via paper - SPANISH
  - Baseline Study Questionnaire – for administration via secure weblink - SPANISH
  - Baseline Study Questionnaire – for administration via phone - SPANISH
- Follow-up Questionnaire (available in 6 formats; content identical in all 6 formats)
  - Follow-up Study Questionnaire – for administration via paper - ENGLISH
  - Follow-up Study Questionnaire – for administration via secure weblink - ENGLISH
  - Follow-up Study Questionnaire – for administration via phone - ENGLISH
  - Follow-up Study Questionnaire – for administration via paper - SPANISH
  - Follow-up Study Questionnaire – for administration via secure weblink - SPANISH
  - Follow-up Study Questionnaire – for administration via phone - SPANISH
- Patient Medication Diary – ENGLISH
- Patient Medication Diary – SPANISH
- Drug Diary Letter – ENGLISH
- Drug Diary Letter – SPANISH
- Informational Flyer – ENGLISH
- Informational Flyer – SPANISH
- Informational Video – ENGLISH (not available in Spanish at this time)

18.0 AFT-28 Statistical Analysis Plan

ALLIANCE FOUNDATION TRIALS, LLC (AFT)

PROTOCOL NUMBER
AFT-28

Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)

CANVAS: Cancer-related VTE Anticoagulation Strategies

Statistical Analysis Plan

Version: 2

Date: January 25, 2021

ClinicalTrials.gov Identifier: NCT02744092

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SIGNATURE PAGE

Protocol Title:	Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in Cancer: A Randomized Effectiveness Trial (CANVAS Trial)
Protocol Number:	AFT-28
SAP Version:	Version 2
Date:	January 25, 2021

Jean Connors, MD Study Chair	Date
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Hajime Uno, PhD Study Statistician	Date

RECORDS ON REVISIONS

Version	Date for creation or modification	Person in charge	Remarks
Ver. 1	December 15, 2020	Hajime Uno	Originally prepared
Ver. 2	January 25, 2021	Hajime Uno	Updated

AFT-28 Statistical Analysis Plan Table of Contents

Glossary of abbreviations

AFT -- Alliance Foundation Trials, LLC
CI -- Confidence Interval
CNS -- Central Nervous System
DOAC -- Direct Oral Anticoagulants
DVT -- Deep Vein Thrombosis
ITT – Intention-to-Treat
LMWH -- Low Molecular Weight Heparin
PE -- Pulmonary Embolism
SD – Standard Deviation
SE – Standard Error
RCT – Repeated Confidence Interval
VTE -- Venous Thromboembolism

1. Introduction

This document describes the statistical analyses and data presentations for the randomized effectiveness of Direct Oral Anticoagulants (DOACs) versus LMWH +/- Warfarin for VTE in cancer. This statistical analysis plan is developed in reference to AFT-28 Protocol Version 7.0 dated January, 20, 2021.

2. Study overview

2.1. Objectives

The primary objective of the study is to compare the effectiveness of anticoagulation with a DOAC (intervention) with LMWH/warfarin (comparator) for preventing VTE recurrence in patients with cancer. The hypothesis is that the benefit of secondary prophylactic anticoagulation with a DOAC is not worse than the benefit from treatment with LMWH/warfarin based on cumulative VTE recurrence reported by patients or their clinicians at 6 months.
The secondary objectives are:

1) To compare the harms of DOAC vs. LMWH/warfarin therapy for cancer patients with VTE based on the cumulative rate of major bleeding at 6 months.
- Hypothesis: The harms from DOAC therapy are not worse than the harms from LMWH/warfarin therapy based on the cumulative rates of major bleeding reported by patients or clinicians at 6 months.

2) To compare the impact of DOAC vs. LMWH/warfarin therapy on the experience and burden of anticoagulation therapy for cancer patients with VTE.
- Hypothesis A: DOAC and LMWH/warfarin therapy are associated with similar overall HRQOL (health-related quality of life) at 3 and 6 months.
- Hypothesis B: DOAC therapy is superior to LMWH/warfarin based on the Anti-Clot Therapy Scale at 3 and 6 months.

3) To compare the impact of DOAC vs. LMWH/warfarin therapy on mortality in cancer patients with VTE
- Hypothesis: The risks of all-cause and cause-specific mortality for cancer patients treated with DOAC therapy are not worse than the risks for those treated with LMWH/warfarin based on survival at 6 months.

2.2. Study Design

The study design is a randomized effectiveness study to evaluate the effectiveness of DOAC therapy compared to usual care with LMWH/warfarin. Eligible patients who accept randomization will be enrolled in the study (the randomized cohort), and they will be randomly assigned either the DOAC therapy group or the usual care group at a 1:1 ratio. Those patients who decline randomization but choose treatment on one of the two study arms will be invited to the study (the preference cohort). The rationale of employing the hybrid study design with the two cohorts is that both cohorts have their own strengths, and they complement each other. Specifically, the randomized controlled design is the most rigorous study design for comparing treatment alternatives. However, it may not capture the effectiveness under the real-world setting because the analysis population is limited to only those patients who accept randomization. On the other hand, the non-randomized study (i.e., the preference cohort) assesses the effectiveness that more likely occurs under real-world circumstances, while the internal validity (i.e., the comparability between the two treatment groups) has to rely on unverifiable assumptions. This hybrid study design will maximize the totality of evidence of comparative effectiveness between the DOAC and usual care. All statistical analyses (details below) will be performed with the randomized cohort and the preference cohort separately, and they will be combined using a

meta-analytic methodology (details below). The results from the randomized cohort will be considered the primary results.

2.3. Eligibility

The protocol (Section 4.0) stated:

- Inclusion criteria
  - Diagnosis of an advanced solid tumor, lymphoma, chronic lymphocytic leukemia (CLL), or myeloma (no time restrictions or limitations) –OR– diagnosis of early stage solid tumor cancer, lymphoma, chronic lymphocytic leukemia (CLL), or myeloma ≤ 12 months prior to study enrollment.
  - Diagnosis of VTE ≤ 30 days prior to study enrollment for which potential benefits of anticoagulation therapy to prevent recurrence of VTE were judged by the treating physician to exceed the potential harms. Diagnosis may be made based on physical exam or imaging studies. Participants with both symptomatic and asymptomatic VTEs are eligible. Any anticoagulation drug/strategy may be used to treat the index VTE; protocol treatment will begin ≤ 14 days after enrollment.
  - Treating physician *intends* to put participant on anticoagulation therapy for at least three months.
  - Age ≥ 18 years.
  - Platelet count is ≥ 50,000/mm^3 (≤ 7 days prior to enrollment).
  - CrCl (Creatinine Clearance) is ≥ 15 ml/min (≤7 days prior to enrollment).

- Exclusion criteria
  - Diagnosis of acute leukemia.
  - Has ever received or is scheduled to receive an Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT).
  - Patients who have ever received an Autologous Hematopoietic Stem Cell Transplantation (autoHSCT) are eligible.
  - Patients who are scheduled to receive an Autologous Hematopoietic Stem Cell Transplantation (autoHSCT) are not eligible.
  - Ongoing, clinically significant bleeding (CTCAE grade 3 or 4).
  - Ongoing therapy with a P-gp inhibitor (e.g., nelfinavir, indinavir, or saquinavir-protease inhibitors for HIV) as these drugs interact with the factor Xa inhibitors.
  - Need for ongoing therapy with: certain antifungals (itraconazole, ketaconazole, voriconazole); rifampin; or certain antiseizure medications (phenytoin, carbamazepine, phenobarbital) at the time of enrollment.
  - Subjects with any other contraindications to anticoagulation or conditions that as judged by the treating clinician would place the subject at increased risk of harm if s/he participated in the study.
  - Pregnant or nursing.

2.4. Randomization and stratification criteria

If an eligible participant was offered randomization and declined to be randomized, then a limited number of participants were allowed to enroll in the Preference Cohort, where the treating physician and patient chose protocol treatment on Arm 1 or Arm 2.

Participants who agreed to be randomized or participants who entered after the closure of the preference cohort were randomized 1:1 to either:

Arm 1 – Intervention Arm, DOAC (choice of rivaroxaban, apixaban, edoxaban, or dabigatran)

Arm 2 – Usual Care Arm, LMWH/warfarin (choice of LMWH with or without a transition to warfarin)

2.5. Sample size justification

The protocol (Section 13.2.4) stated that:

- As of April 28, 2020, the study has enrolled a total of 808 patients. Of the 808, 668 were enrolled in the randomized cohort. When we discontinue the patient enrollment now, the total sample size is expected to be around 810 depending on the exact date of formal closure. With this sample size, the power of noninferiority test already reaches 90% (See Table). For superiority, it is slightly below the 80% target power at 75%. The expected length of confidence interval (CI) for the difference in event rate is now 6.1% with 808 patients, and it would have been 5.8% with the planned total sample size (N=890). This suggests that the gain in the precision may be marginal. Given the challenges to continued accrual in the setting of the COVID-19 pandemic and the recently reported results of the Caravaggio study we propose revision as follows.
-

Table: Power calculation for the primary analysis

Date	N (Randomized Cohort)	N (total)	Length of CI for difference	Power	
				Noninferiority	Superiority
Revised Statistical Analysis Plan	668	808	6.1%	0.900	0.756
Originally Planned Goal	750	890	5.8%	0.927	0.797

Note that the termination of the new enrollment to the CANVAS trial therefore was approved by the AFT DSMB in April 2020 before reaching the original proposed 890 patient accrual mark. Upon formal study closure at all sites, the final total sample size was 811 (140 in the preference cohort, 671 in the randomized cohort).

3. Analysis methods and presentation

3.1. General principles

Analysis will be performed on the preference cohort and the randomized cohort separately. Where appropriate, variables will be summarized descriptively (frequency counts and percents for categorical variables, and counts, means, standard deviations (SD), medians, minimums, maximums, etc., for continuous variables) for two treatment groups – DOACs and Control. The primary analysis cohort is the randomized cohort. The secondary analysis cohort is the preference cohort. Using meta-analysis technique, the results from two cohorts will be combined.

We will construct 90% two-sided confidence intervals (CI) for the between-group comparisons for the analyses of VTE, bleeding, and mortality. A 90% two-sided CI corresponds to conducting a statistical test at a one-sided 5% significance level. For the other analyses, all confidence intervals, statistical tests, and resulting p-values will be reported as two-sided and assessed at the 5% significance level. If the computed lower confidence bound for proportion variables is less than –1, then the lower bound is defined as –1. If the computed upper confidence bound for proportion variables is greater than 1, then the upper bound is defined as 1.

3.2. Definition of analysis populations

Intention-to-Treat (ITT) population
The intention-to-treat population for the randomized cohort includes all randomized subjects. The corresponding population for the preference cohort consists of all patients who would not be randomized but participated in this study. The corresponding population for the full cohort consists of all randomized subjects and all subjects in the preference cohort. In the analyses with the ITT populaiton, we peformed the analyses by group, using the assinged treatment group indicator regardless of whether the subject recieved the assigned treatment or not.

Modified Intention-to-Treat (ITT) population (Primary analyses)
Based on the data review performed before conducting the final analysis, we found that quite a few subjects in this pragmatic trial did not receive treatment according to their assigned group. In the ITT population, those patients who received treatment in the group opposite to the one to which they were randomized would also be included in the analysis. Based on the concern that these subjects could cause a potential bias toward the noninferiority claim with the ITT analysis, we have defined a modified ITT population. In order to be conservative with regard to testing the non-inferiorty hypothesis, the primary analyses will rely on the modified ITT population. The modified ITT population includes all subjects who received a study drug according to their assigned treatment group and participated in this study.

The modified ITT population for the randomized cohort includes all randomized subjects who received at least one dose of the anti-coagulation treatment strategy to which they were assigned. The preference modified ITT population includes all non-randomized subjects who received the anti-coagulation treatment which they preferred subsequet to informed consent to study participation. The full modified ITT population includes the sum of the two aformentioned categories (randomized cohort and preference cohort).

Per-protocol population
The per-protocol population includes those patients who received a study drug of the assigned treatment group and do not have any major protocol violations.

The randomized per protocol population includes those subjects who received a study drug according to the randomized treatment assignement and do not have any major protocol violations. The preference per protocol population includes those subjects who were not randomzied and received a study drug according to the subject's preference and do not have any major protocol violation. The full per protocol population is the sum of the two aformentioned categories.

Safety population

The safety populations are identifical to the modified ITT populations.

3.3. Disposition of study subjects

Following the CONSORT guideline[1] a CONSORT diagram will be generated to describe the patient population by cohort with descriptions of the numbers of participants in the preference and randomized cohorts displayed side by side.

3.4. Baseline demographic and disease characteristics

Baseline patient characteristics and disease characteristics listed below will be summarized using descriptive statistics by group. The two-sample Wilcoxon test will be used for between-group comparisons of continuous variables and ordered categorical variables, and Fisher's exact test will be used for nominal categorical variables.

List of the variables:

- Age at enrollment [year]
- Age category (<65, >=65 year old)
- Sex (Male/Female)
- Race (Native American or Alaska Native/Asian/Black or African American/Native Hawaiian or other Pacific Islander/White/Unknown)
- Ethnicity (Hispanic or Latino/Not Hispanic/Unknown)
- Height [cm]
- Weight [kg]
- BMI
- Education level (Grade school or less/high school or GED/Some vocational, business or trade school/some college/college/some graduate school/graduate or professional degree)
- Whether out-of-pocket costs of anti-clotting drugs affect decision to participate in the study (not at all/a little/moderate/quite a bit/extremely)
- Payment (Private insurance/Medicare/Medicaid/Military or Veterans Sponsored/Self Pay/ Other/Unknown)
- ECOG performance status (0/1/2/3/4)
- Smoking status (current/former/never)
- Cancer ever metastasized (Yes/No)
- HighlyThrombogenetic Tumors (Yes/No)
- Indwelling Central Venous Catheters (Yes/No)
- Thrombocytopenia (Yes/No) (<150,000/mm3)
- Creatinine Clearance [ml/min] (Gender-specific Normal/abnormal)
- Albumin [g/dL] (<3.5mg/dl vs. >=3.5mg/dl)
- Self described global health status at baseline (excellent/very good/good/fair/poor)
- Current cancer Type (solid cancer vs hematologic cancer)
- Current cancer Subtype (Leukemia/Lymphomas/Blood Disorders, Breast, Gastrointestinal and Digestive, Gynecologic, Head and Neck, Neurological (Brain), Sarcoma, Skin/Melanoma, Thoracic (Chest/Lung), Genitourinary, Other)
- AJCC cancer stage at diagnosis (0, I, II, III, IV, Not applicable)
- Blood clot type (PE, DVT, Both, Unknown)
- The part(s) of the body where the blood clot found
    - Lung (Yes/No)
    - Leg (Yes/No)
    - Arm (Yes/No)

  - Other (Yes/No)
- Site of index VTE diagnosis (inpatient hospital stay/outpatient appointment/emergency department/home/other)
- Site of index VTE first treatment (inpatient hospital stay/outpatient appointment/emergency department/home/other)
- First index VTE treatment prescribed (Warfarin/Dalteparin/Enoxaparin/Fondaparinux/Heparin/Other oral medication/Other injectable medication/Unknown)
- Previous VTEs and the number of prior VTEs (No, 1, 2, 3+)
- Bleeding at baseline (None, Mild, Moderate, Severe)

3.5. Primary endpoint evaluation

3.5.1. Primary endpoint

The primary endpoint is cumulative VTE recurrence reported by either patients or their clinicians at 6 months. A recurrent VTE is synonymous with the cumulative incidence of any VTE irrespective of the anatomic site. Note that we will analyze the VTE recurrent event rate at 6 months but the data we will use to assess this primary endpoint is not a dichotomous variable that indicates the presence/absence of cummulative VTE recurrent events at 6 months. The analysis variable we will use for the primary endpoint is time from enrollment to occurrence of a VTE recurrent event. We will estimate the VTE recurrent event at 6 months using a time-to-event analysis with this analysis variable, where deaths are handled as competing risks and lost-to-followup patients are handled as censored observations (see Section 3.5.2.1 for details). This approach accounts for censored observations more appropriately than an analysis using a dichotmous variable, whereas it yields the same result if there are no censored observations.

3.5.2. Analysis for the primary endpoint

3.5.2.1. Primary analysis

The primary aim of this study is to compare the intervention and comparator arms with respect to their ability to prevent recurrent VTE. Because the intervention (DOAC therapy) is more easily administered than the comparator (usual care with LMWH warfarin), DOAC is expected to have higher adherence and therefore decreased incidence of VTE. Accordingly, a noninferiority design with a superiority alternative is preferred, as described by Friedlen et al.[2] The primary analysis will test the noninferiority of the DOAC therapy with the primary analytic cohort (modified ITT population of the randomized cohort). If noninferiority is demonstrated, superiority of the DOAC therapy will be tested.

Because VTE is often a proximate cause of death in cancer patients' unexplained sudden demise, but diagnostic procedures are rarely performed (post-mortem scans, autopsies, etc.), we considered VTEs that were clinically significant as the primary outcome on the basis of an antemortem diagnosis. Separately, we looked at all-cause deaths because deaths from cancer and deaths from VTE are difficult to distinguish. Cancer patients routinely die at home and it is not possible to determine whether the proximate cause of death was a VTE, progression of tumor or some other cause. Indeed, the cause of many deaths in cancer patients is multifactorial. We will estimate the cumulative incidence of recurrent VTE at 6 months using standard competing risk analysis methods[2], where death will be treated as a competing risk. We calculate the difference in the 6 months incidence rate between groups and the corresponding 0.90 confidence interval (CI).

1) Noninferiority test of DOAC

The hypothesis for testing the noninferiority of the DOAC strategy is that the difference in the primary endpoint at 6 months is no greater than a noninferiority margin of 3% for the intervention-comparator. This noninferiority margin was selected based on what is acceptable to patients based on patient-stakeholder input as well as on input provided by clinicians

To confirm the noninferiority hypothesis, we will construct a two-sided 90% confidence interval (CI) for the difference in the cumulative incidence of the primary endpoint at 6 months (180 days). If the upper bound of the CI is less than 3%, we will conclude that the DOAC management strategy is non-inferior to the LMWH/warfarin strategy for management of VTE in patients with cancer.

2) Superiority test of DOAC

If noninferiority of DOAC is demonstrated, a superiority test of DOAC will be performed using a one-sided 0.05 significance level and the same two-sided 90% CI for the difference in the event rate of the primary endpoint at 6 months as used for the noninferiority test. When the upper bound of the CI is less than 0, we will conclude that DOAC therapy is superior to LMWH/warfarin in terms of VTE prevention. Because we will perform the superiority test only after the noninferiority of DOAC is demonstrated, the overall type I error rate is maintained at the 0.05 level (one-sided) without splitting alpha.[3]

3.5.2.2. Planned Interim Analyses

This study design incorporates several interim analyses and one final analysis for the comparison of the primary endpoint. A 90% two-sided repeated confidence interval (RCI)[4] for the difference in the cumulative incidence rate of VTE at 6 months (DOAC minus Usual Care) between two arms was estimated. We use the critical values based on the Lan-DeMets error spending function[5] corresponding to the truncated version of O'Brien-Fleming boundaries.[6]

Prior to the final analysis, four interim analyses were conducted on September 7, 2018, March 22, 2019, September 9, 2019, and March 25, 2020. Given these interim analyses, the critical value for the final analysis will be 1.710, which corresponds to a one-sided 0.0436 alpha. The confidence coefficient of the 90% two-sided RCI will be 91.28% for the final analysis.

3.5.2.3. Secondary analyses of the primary endpoint

1) Analysis with other summary measures

The absolute difference in 6-month event rate based on the cumulative incidence function (CIF) is the primary summary measure of the between-group difference. As a secondary analysis, we will calcuate a subhazard ratio using the Fine and Gray model.[7] We will construct 0.90 CIs for these measures.

2) Alternative way to handle deaths

In the primary analysis, we handle deaths as competing risks and estimate the recurrent VTE rates by the CIF approach. As a secondary analysis, we will handle deaths as censored observations and estimate the recurrent VTE event rates by the Kaplan-Meier method. We will calculate the hazard ratio and difference in the event rate at 6 months and corresponding 0.90 CIs.

3) Sensitivity Analyses including data from the preference cohort
This study allowed a limited number of participants to enroll in the preference cohort if an eligible participant declines randomization. The Preference Cohort Closing Rules were pre-specified in Section 13.2.2 in the study protocol to specify the maximum number of participants enrolled in the preference cohort and to avoid an extreme imbalance of the number of participants between two groups. The results of monthly data monitoring in June 2017 observed the pre-set imbalance criteria in between arm selection. The enrollment to the preference cohort was thereforeclosed in December 2017, after 140 patients had enrolled in it.

First, we will compare characteristics between the preference and randomized cohorts to assess potential heterogeneity between the two cohorts. Fisher's exact test will be used for nominal categorical variables, and two-sample Wilcoxon tests will be used for ordered categorical or continuous variables.

We will estimate the difference in VTE event rate at 6 months and its standard error from the preference cohort, using a propensity score approach to adjust for potential treatment selection.[8] We will then combine the result with that from the randomized cohort, using a weighted average. An optimal weight (i.e., the reciprocals of the variance) will be used. The resulting estimate for the difference in VTE event rate and 90% CI can be considered an overall average treatment effect of DOAC across the full cohort. In no circumstance will analyses of the full cohort be presented as primary.

4) Analysis by type of VTE recurrence
We will also conduct the same analyses for each of the following subtypes of VTE recurrence.
1) Pulmonary embolism (PE) with or without deep vein thrombosis (DVT)
2) DVT without PE

5) Adjusted analyses
We will perform adjusted analysis to estimate the adjusted treatment effect, using generalized linear mixed-effects models with the logit link. Censored observations will be handled by the inverse probability censoring weight technique. [9] The participating sites will be included as random-effects. [10] Those baseline characteristics variables (see 3.4) whose distributions are not balanced between two groups ($p<0.05$) in the randomization cohort will be included as fixed-effects in the models for adjustment.

6) Sensitivity Analyses using the ITT and the per protocol populations.
Sensitivity analyses will be performed with alternative cohort specification.
We will repeat all the analyses using the ITT population and then using the per-protocol population.

3.6. Secondary endpoint evaluation

3.6.1. Secondary endpoints

- Cumulative incidence of major bleeding reported by either patients or clinicians at 6 months
- Cumulative incidence of all bleeding events and bleeding according to its severity in the following categories:1) major bleeding, 2) clinically significant non-major and 3) nuisance
- Cumulative incidence of death at 6 months
- Overall HRQOL at 3 and 6 months
- Overall score on the Anti-Clot Therapy Scale at 3 and 6 months

3.6.2. Analyses for secondary endpoints

1) Cumulative rates of major bleeding reported by patients or clinicians at 6 months (grade 3, 4, or 5)

We will repeat the analogous analyses as performed for the primary endpoint (see 3.5.2). The primary analysis plan for major bleeding, fatal or non-fatal, is also based on the sequential evaluation of noninferiority and superiority. We will construct a two-sided 90% CI for the difference in the cumulative incidence rate for the composite outcomes of major bleeding and death. If the upper bound of the CI is less than 2.5%, we will conclude that DOAC is noninferior to LMWH/warfarin in terms of major bleeding. The same secondary analyses as planned for the primary endpoint will be performed. In contrast to clotting, fatal bleeding events are usually clinically manifest and recorded and therefore can be distinguished.

2) Cumulative incidence of all bleeding events reported by patients or clinicians at 6 months in the following categories: 1) major bleeding (Grade >=3), 2) clinically significant non-major (Grade 2); and,3) nuisance bleeding (Grade 1)

Clinically significant non-major bleeding is defined as Grade 2 Nuisance bleeding is defined as Grade 1 according to the NCI CTCAE criteria. We will perform the same analyses as described for major bleeding.

3) Mortality

Time from randomization to death from any cause is a secondary endpoint. The study is powered to confirm the primary hypothesis for recurrent VTE; we do not anticipate enough power to perform a confirmatory analysis for all-cause mortality. We will instead focus on providing quantitative information for the between-group difference for this endpoint. We will describe the survival time distribution by treatment group using the Kaplan-Meier method. Also, we will compare the restricted mean survival times (RMST)[11] between groups. The truncation time point for calculating the RMST will be 6 months, which will give us an estimate of 6-month lifetime expectancy for each group. We will estimate the difference in RMST and the corresponding 90% CI. The hazard ratio for death and its 90% CI will also be calculated if the proportional hazards assumption is reasonable. The determination of the violation of the proportional hazards assumption will be based on a significant p-value (<0.05) for the Grambsch and Therneau test.[12]

4) The Patient-Centered Experience of Anticoagulation QOL and Burdens

i) Health Related Quality of Life (SF-12) at 3 and 6 months

For SF-12, the primary analysis variable is the difference in the SF-12 mean change score from baseline. We will consider 2-point differences as clinically meaningful. We will use multiple imputations to handle missing observations.[13] First, we will create 10 complete datasets, imputing missing values using chained equations, where we include measurements at baseline, 3 months, and 6 months. Second, we will estimate mean changes and the standard errors for each of the 10 complete sets. We will then use Rubin's method to derive an estimate for the difference in the mean change score

between two groups. Using the resulting estimate and the standard error, we will perform a Z-test to evaluate equality of SF-12 scores between groups.

ii) Anti-Clot Treatment Scale (ACTS) score at 3 and 6 months
For ACTS score, the primary analysis variables are the ACTS Burdens total score and the ACTS Benefits total score at month 6. We will consider 2-point differences as clinically meaningful. To minimize potential bias due to missing observations, we will allow and include surrogate estimates for all 3 patient-reported outcome assessments. Next, we will use multiple imputation to handle missing observations. First, we will create 10 complete datasets, imputing missing values using chained equations, where we include measurements at baseline, 3 months, and 6 months. Second, we will estimate mean changes and the standard errors for each of the 10 complete sets. Lastly, we will integrate the results using Rubin's method.

3.7. Other/Persistence with treatment endpoints

- Performance status
  We will use the two-sample Wilcoxon test to evaluate between-group differences in ECOG PS.
- Cumulative rates of remaining on any anti-coagulation therapy at 3 and 6 months
- Cumulative rates of remaining on the assigned (and/or selected in the case of the preference cohort) anti-coagulation therapy at 3 and 6 months.
-

3.8. Safety endpoint evaluation

3.8.1. Safety endpoints

- Major bleeding (primary protocol safety endpoint)
- Clinically significant non-major bleeding
- Any bleeding (major bleeding and clinically significant non-major bleeding and nuisance bleeding)
- Other Serious Adverse Events

  For this trial, "Expedited Serious Adverse Event" reporting is required using the SAE Report Form in REDCap. Adverse event reporting begins at enrollment and should continue until 30 days after the last administration of on-study protocol treatment. SAEs for other endpoints are reported via the following guidelines:
  - Grade 1 or 2 adverse events that resulted in hospitalization for 24 or more hours, or
  - Grade 3, 4, or 5 adverse events regardless of hospitalization

3.8.2. Analyses for safety endpoints

The analysis plan for major bleeding and any bleeding are outlined in section 3.6.2. Incidence of all other SAEs will be summarized by cohort, arm, grade, and type of SAE. Fisher's exact test will be performed to compare the event rates.

3.9. Subgroup Analyses

We will perform subgroup analyses to investigate the potential heterogeneity of treatment effects. For each subgroup, we will perform the same analyses described in the previous sections. The treatment effect by subgroup will be summarized by point estimates and corresponding 90% confidence intervals. We will create forest plots to display those results. This analysis will be performed with an exploratory purpose; we will not adjust for multiple comparisons.

First, we will focus on the 3 key subgroups described below because these groups are common, and decision making in these contexts is challenging for oncologists and patients. These 3 subgroups represent populations of particular interest for clinical decision makers.

3.9.1. Pre-specified subgroup 1: Patients with Highly Thrombogenic Tumors

We anticipate that at least 300 patients with lung (NSCLC and small cell), pancreas, esophagogastric and ovarian cancers are represented in the study sample. These patients have an even higher risk of VTE than cancer patients in general. Based on anticipated higher adherence rates to DOAC therapy and the likelihood of warfarin failures in the LMWH/warfarin arm, we anticipate a slight advantage for DOACs over the standard care arm. As planned for the full cohort analysis, we will only test for superiority in the subgroup if noninferiority is met.

3.9.2. Pre-specified subgroup 2: Indwelling Central Venous Catheters

We anticipate that a subgroup of approximately 500 study participants will have an indwelling central venous catheter in place at the time of enrollment. This recruitment should not be challenging given how commonplace use of these catheters has become in routine oncology practice. The rate of VTEs is expected to be slightly higher for patients with a central venous catheter due to the excess risk of upper extremity clots.

3.9.3. Pre-specified subgroup 3: Thrombocytopenia

We will consider the subgroup of participants with baseline platelet counts less than 150,000/microliter. Thrombocytopenic cancer patients face high risk of VTE but also face higher risks of bleeding. In this setting, the choice of anticoagulation strategy is challenging.

3.9.4. Other preplanned subgroups

We will perform the same analysis for the following subgroups with an exploratory purpose.

- Sex (Male, Female)
- Age (below 65, equal or greater than 65)
- Participants with central nervous system (CNS) tumor involvement
- Participants with liver metastases
- Participants with albumin <3.5mg/dL
- Participants treated with bevacizumab
- Participants incidentally detected VTE on routine imaging studies (versus symptomatically detected VTE)
- Participants with metastatic disease (versus completely resected disease or no radiographic evidence of tumor)
- Participants with >80% days of persistence with anticoagulant therapy (vs. >50-80% vs. <=50%) by participant estimate

- Participants with >80% days of persistence with anticoagulant therapy (vs. >50-80% vs. <=50%) by medical record abstraction/dose refills
- Solid tumors versus hematologic malignancies

3.10. Software

The statistical analyses will be performed with R version 4.0.2, Stata version 16, and SAS version 9.4.

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