DF/HCC Protocol #: 15-547

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TITLE: A randomized, phase II study of weight-based versus standard dose enoxaparin thromboprophylaxis in high-risk hospitalized cancer patients.

Coordinating Center: Beth Israel Deaconess Medical Center

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Study is Exempt from IND Requirements per 21 CFR 312.2(b).

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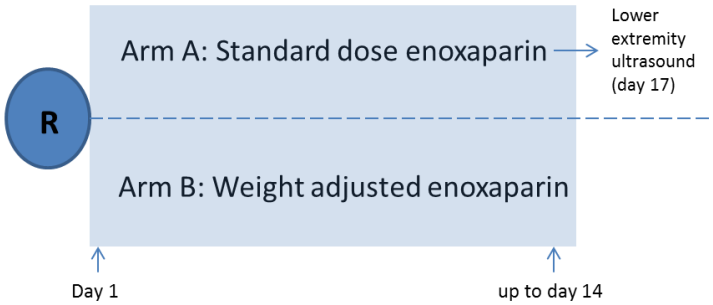
SCHEMA


Arm A: Standard dose enoxaparin
Lower extremity ultrasound (day 17)
R
Arm B: Weight adjusted enoxaparin
Day 1
up to day 14

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1. OBJECTIVES

1.1 Study Design

This is a 2-arm, randomized, double-blinded multi-center phase II trial to estimate the cumulative incidence of venous thromboembolic events (VTE) and major hemorrhage in hospitalized cancer patients receiving enoxaparin thromboprophylaxis. Hospitalized cancer patients considered to be at high risk of thrombosis (based on malignancy diagnosis and Padua risk factors) will be randomized to standard dose enoxaparin daily versus weight-adjusted enoxaparin daily for up to 14 days.

1.2 Primary Objectives

- The primary objectives of the study are to estimate the cumulative incidence of VTE and major hemorrhage in hospitalized cancer patients receiving standard dose or weight-adjusted enoxaparin.

1.3 Exploratory Objectives

- Compare rates of symptomatic VTE between enoxaparin arms at day 14
- Evaluate the performance of clinical scoring models (ie. Padua, IMPROVE, and Khorana Score) in predicting thrombotic risk in hospitalized cancer patients
- Assess the prognostic value of biomarkers (e.g. D-dimer and microparticles) to predict thrombosis in hospitalized cancer patients

2. BACKGROUND

2.1 Study Disease(s)

Venous thromboembolism is estimated to account for up to 5% of all deaths during hospitalization.[1] Recognizing the burden on healthcare and the preventable nature of venous thromboembolic events during hospitalization, U.S. Government agencies are working to improve the rates of prescribed thromboprophylaxis. The Agency for Healthcare Research and Quality identified thromboprophylaxis as the number one patient safety practice[2], the Surgeon General issued a *Call to Action[3]*, and the Centers for Medicare & Medicaid Services is targeting hospital thromboprophylaxis in a national health-care quality initiative. Major professional organizations including the American Society of Clinical Oncology, National Comprehensive Cancer Network, American College of Chest Physicians, and European Society of Medical Oncology have all issued strong recommendations for the prescription of pharmacologic thromboprophylaxis of hospitalized cancer patients.[4-7] And yet, despite the association between cancer-thrombosis and increased in-hospital cancer mortality, the absolute benefit, toxicity and even appropriate dosing of routine thromboprophylaxis in cancer patients is unknown. In the three phase III registration trials comparing low molecular weight heparins with placebo in hospitalized medical patients, only 6% of patients carried a diagnosis of cancer and there was no statistical benefit for thromboprophylaxis in the subgroup analysis of cancer patients included in these trials.[8] This phase II trial will establish point estimates on the risk of

VTE and hemorrhage in preparation for a planned phase III clinical trial to assess the risks and benefits of anticoagulation in cancer patients at increased risk for thrombosis.

Risk factors for thrombosis in hospitalized cancer patients
In analysis of a large hospital discharge database that included over 1 million cancer patients, the overall incidence of venous thromboembolic events (VTE) was 4.1% per hospitalization with considerable variation according to presence of concomitant thrombotic risk factors.[9] For instance, in 26,118 patients with pancreatic cancer the rate of VTE was 8.1% per hospitalization whereas the rate was 1.4% in the 50,898 patients with head and neck malignancy. Other higher risk tumors included ovary (5.6% rate of VTE), lung (5.1%), stomach (4.9%), and non-Hodgkin lymphoma (4.6%). Independent risk factors for thrombosis during hospitalization included primary site of cancer, age, chemotherapy, and comorbidities (e.g. infection, pulmonary, renal disease).

Prediction models have been developed to identify which populations of hospitalized patients are at highest risk of thrombosis but these have not been specifically developed for hospitalized cancer populations. In the widely cited Padua Prediction Score, independent risk factors for VTE include cancer, prior history of VTE, reduced mobility, hereditary thrombophilia, recent surgery or trauma, obesity, elderly, and comorbidities (e.g. infection, acute coronary syndrome, respiratory failure).[10] Among the 659 low risk patients (Padua Score of <4) not receiving pharmacologic thromboprophylaxis, only one patient (0.2%) was diagnosed with VTE during hospitalization. By comparison, the rate of thrombosis was 7.5% among the 469 high-risk patients (Padua Score $\geq$ 4).

Risk-benefit assessment for thromboprophylaxis for hospitalized cancer patients
In a recent systematic review and meta-analysis of cancer patients enrolled in randomized phase III clinical trials.[8] Only 307 cancer patients were enrolled among the three major registration clinical trials involving low molecular weight heparins (or fondaparinux) versus placebo. The pooled relative risk of VTE was 0.91 (95% CI, 0.21-4.0) with two trials demonstrating a non-significant reduction of thrombosis in cancer patients while the third trial demonstrated a statistically significant increase in thrombosis in patients receiving thrombopropylaxis with fondaparinux. Fondaparinux has been shown previously in randomized clinical trials to prevent thrombosis following cancer surgery and thus these results are unlikely to point simply to the ineffectiveness of a single thromboprophylactic agent. In all studies the incidence of thrombosis was higher in the cancer subgroup receiving thromboprophylaxis compared with non-cancer patients. It is evident that anywhere from 1 in 5 to 1 in 20 hospitalized cancer patients are diagnosed with VTE despite receiving recommended thromboprophylaxis.

2.2 Study Agent (Enoxaparin)

Enoxaparin is a low molecular weight heparin with antithrombotic properties approved by the Federal Drug Administration for prevention of deep vein thrombosis following abdominal or orthopedic surgery and in medical patients with restricted mobility during acute illness.

Enoxaparin administered subcutaneously achieves steady-state activity levels predicted by single-dose pharmacokinetics. After repeated subcutaneous administration of 40mg once daily,

the steady state is reached on day 2 with an average exposure ratio of 15% higher than after a single dose. Enoxaparin is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose. In the elderly, the apparent clearance of enoxaparin following multiple subcutaneous doses is similar to younger subjects. A linear relationship exists between activity and creatinine clearance.

Standard dose enoxaparin for thromboprophylaxis in medical patients:
In a double blind multicenter parallel group study, enoxaparin at 20mg or 40mg once a day for 14 days was compared to placebo in medical patients with severely restricted mobility.[11] Patients were enrolled with the following diagnosis: congestive heart failure (NYHA class III or IV), acute respiratory failure or complicated chronic respiratory insufficiency, acute infection, or acute rheumatic disorder. A total of 1073 patients were treated on the study for a maximum of 14 days (median 7 days). Enoxaparin administered at 40mg once daily was associated with a significant reduction in thromboembolic events compared with placebo (5.5 vs 14.9, P<.001). The lower (20mg) dose of enoxaparin was not associated with a reduction in thromboembolic events (12.2%). Enoxaparin (40mg) was well tolerated with 6 of 360 patients suffering a major hemorrhagic event compared with 4 of 362 treated with placebo. There were 8 cases of thrombocytopenia in the placebo group and 2 in the enoxaparin (40mg) treated group. There were no significant differences in the groups for any other adverse outcomes.

Modified dose enoxaparin thromboprophylaxis in cancer patients.
The pharmacokinetic profile of low molecular weight heparins are known to be dependent on body weight.[12] Compared with fixed dose enoxaparin at 40mg, weight adjusted dose of enoxaparin of 1mg/kg yields significantly greater peak anti-Xa activity, anti-IIa activity and inhibition of thrombin generation.[12, 13] Notably, there is randomized trial data to support the safety and efficacy of enoxaparin at 1mg/kg daily for thromboprophylaxis in cancer patients. The CONKO-004 trial randomized over 300 patients with advanced pancreatic cancer to chemotherapy alone or chemotherapy with enoxaparin 1mg/kg daily for 3 months. At 3 months, they observed an approximate 85% risk reduction in the incidence of VTE in the arm randomized to intermediate dose enoxaparin (P=0.001) without an increase in major hemorrhage (P=1.0).[14]

2.3 Rationale

Based on the available evidence, it is apparent that an accurate assessment of risk versus benefit for primary thromboprophylaxis of hospitalized cancer patients is not possible. It is also evident that hospitalized cancer patients commonly receive pharmacologic thromboprophylaxis without attention to the presence or absence of thrombotic risk factors. In highest risk cancer patients, current pharmacologic regimens are inadequate with as many as 20% patients suffering from thromboembolic events. The principle goals of this phase II clinical trial are to establish a more accurate point estimate of rate of VTE in high risk cancer patients receiving standard, fixed-dose low molecular weight heparin thromboprophylaxis and to develop a point estimate of hemorrhage using intermediate-dose enoxaparin prophylaxis in higher risk patients.

2.4 Correlative Studies Background

Evaluation of Padua, IMPROVE, and Khorana risk models in hospitalized cancer patients.
Published risk models have been developed to identify a collective group of risk factors that identify patient populations considered to be at sufficiently high risk of thrombosis to warrant thromboprophylaxis. The IMPROVE scoring model was developed using a database of 15,000 patients from 12 countries. A multiple regression analysis identified independent risk factors for VTE in acutely ill hospitalized medical patients.[15] The incidence of thrombosis following hospitalization was 11% in patients with IMPROVE scores $\geq$5. The four independent risk factors at admission comprising the scoring model are: previous history of VTE (3 points), known thrombophilia (3 points), age>60 years (1 point), and cancer (1 point). The Khorana score was developed for cancer outpatients receiving chemotherapy. Abnormal pre-chemotherapy complete blood count indices (white blood cell > $11x10^9$/L, hemoglobin < 10 g/dL, and/or platelet count > $350x10^9$/L) are independently associated with thrombosis in cancer outpatients and are elements of the Khorana risk score.[16-18] In order to evaluate the performance of the Khorana score in predicting thrombotic risk for hospitalized cancer patients, we will calculate the Khorana score utilizing laboratory data (e.g. blood counts) upon admission. The Khorana score will be calculated for all patients following completion of the study during the data analysis phase. As this scoring system was not specifically developed for cancer patients, we will explore whether improved specificity can be achieved while retaining sensitivity to identify patients at greatest risk for VTE.

Microparticles and risk of thrombosis in cancer patients.
Microparticles are vesicular structures measuring less than 1μm in size and are derived from a number of cells within the vascular compartment including leukocytes, platelets, red blood cells, and endothelial cells.[19] Initial interest in exploring the association between tissue factor bearing microparticles and thrombosis was based on observations that tissue factor bearing microparticles bind to a developing thrombus and play a role in fibrin propagation in vivo.[20] Utilizing an impedance-based flow cytometer specifically modified for microparticle measurement, we observed that tissue factor bearing microparticles are elevated in cancer patients diagnosed with VTE (adjusted OR 3.72, P=0.01) and appear to be derived from the underlying tumor.[21] The association between tissue factor bearing microparticles and cancer associated thrombosis has now been reported by several groups, including in a mouse model of vascular injury.[22-25] A randomized, multi-center phase II clinical trial (MicroTEC Trial) substantiated the prognostic role of tissue factor bearing microparticles and VTE in cancer patients.[26] The cumulative incidence of VTE in cancer patients with elevated tissue factor bearing microparticles randomized to observation was 27% compared with 5% in those receiving enoxaparin (Gray's test P=0.06) while 7.2% of those cancer patients with low levels of tissue factor bearing microparticles were diagnosed with VTE without thromboprophylaxis. Notably, the cumulative incidence of VTE was 43% at 2 month in patients with both elevated levels of D-dimer and tissue factor bearing microparticles compared with 4.2% for all other study subjects (Gray's test P value = 0.0001).[26] Planned correlative studies include the measurement of tissue factor bearing microparticles as well as the population of tissue factor bearing microparticles co-expressing P-selectin glycoprotein 1(PSGL-1).

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed diagnosis of solid tumor malignancy, lymphoma, or multiple myeloma

3.1.2 Cancer diagnosis or received treatment (chemotherapy or radiotherapy) for malignancy within the previous 6 months

3.1.3 One or more Padua-based risk factor:

- History of previous venous thromboembolic event (excluding superficial vein thrombosis)
- Reduced mobility (ECOG performance status 3 or 4, see Appendix A)
- Established hereditary thrombophilia (e.g. Factor V Leiden, G20210 prothrombin mutation, protein C or S deficiency, antithrombin deficiency).
- Recent surgery within the last 30 days
- Age $\geq$ 70 years
- Congestive heart failure (NYHA class III or IV)
- Complicated respiratory insufficiency (defined as an increased requirement for supplementary oxygen of at least 2L)
- Acute myocardial infarction or ischemic stroke
- Obesity (BMI $\geq$ 30)
- Receiving hormonal agents (e.g. tamoxifen, estrogen, testosterone)
- Acute infection (i.e. requiring antimicrobial therapy)

3.1.4 Age $\geq$ 18 years

3.1.5 Life expectancy of greater than 30 days

3.1.6 Platelet count $\geq$ 100,000/mcL

3.1.7 Creatinine < 1.5 mg/dL or estimated creatinine clearance $\geq$ 50 mL/min/1.73 m^2

3.1.8 Ability to understand and the willingness to sign a written informed consent document

3.1.9 Weight between 50kg to 130 kg.

3.2 Exclusion Criteria

3.2.1 History of allergic reactions attributed to heparin or low molecular weight heparin

3.2.2 Active bleeding or otherwise considered high risk for hemorrhage (e.g. known acute gastrointestinal ulcer)

3.2.3 Any history of significant hemorrhage (requiring hospitalization or transfusion) within the last 6 months (excluding hemorrhage during operative procedure).

3.2.4 History of heparin induced thrombocytopenia

3.2.5 Presence of coagulopathy (PT or PTT> 1.2 x upper limit of normal)

3.2.6 Known diagnosis of disseminated intravascular coagulation

3.2.7 Currently receiving therapeutic anticoagulant therapy or dual antiplatelet therapy (eg. aspirin and clopidogrel)

3.2.8 Uncontrolled arterial hypertension (systolic blood pressure > 200mmHg, diastolic >110mmHg)

3.2.9 Active peptic ulcer disease

3.2.10 Bacterial endocarditis

3.2.11 Received any type of pharmacologic thromboprophylaxis (e.g. low molecular weight heparin or heparin) for >48 hours during current hospitalization

3.2.12 Known brain metastases

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

Following registration, QACT office will perform randomization to Arm A or Arm B of enoxaparin. Randomization arm will be communicated directly through QACT to the research pharmacy at Beth Israel Deaconess Medical Center. For participants enrolled at Cleveland Clinic, a representative from the BIDMC Research Pharmacy will forward the randomization assignment to the dedicated contact at the Cleveland Clinic Research Pharmacy.

Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at xxx-xxx-xxxx. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, research pharmacy, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Beth Israel Deaconess Medical Center by the Study Coordinator.

Following registration, participants should begin protocol therapy within 24 hours. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not

receive protocol therapy following registration, the participant's registration on the study must be canceled and they will be replaced. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and sent to::

- Copy of eligibility documentation
- Signed eligibility and consent physician note
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist

The research nurse or data manager at the participating site will then call *xxx-xxx-xxxx* or e-mail to verify eligibility. To complete the registration process, the Coordinator will

- register the participant on the protocol with the QACT
- fax or e-mail the participant study number, and if applicable the dose treatment level to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration

NOTE: Registration and randomization with the QACT can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment Overview:

Eligible participants will be randomized to standard dose enoxaparin at 40 mg once daily (Arm A) versus weight-based enoxaparin at 1 mg/kg once daily (Arm B). On study enoxaparin will be administered for up 14 days during hospitalization. Physicians and participants will be double-blinded to enoxaparin dosing during hospitalization (or up to 14 days). After the day 14 assessment, treatment arms will be un-blinded in order to appropriately schedule a bilateral lower extremity ultrasound for participants enrolled onto Arm A at day 17.

Note that patients who are discharged and re-admitted prior to day 14 will resume study procedures and enoxaparin administration per initial randomization.

Arm A:

Participants will receive enoxaparin 40 mg subcutaneously once daily.

Arm B:
Participants will receive enoxaparin at 1mg/kg subcutaneously once daily with maximum dose of 100 mg daily. Participants who weigh more than 100kg will be capped at 100mg.

Participants who receive at least one dose of treatment post-randomization will be considered evaluable for the study.

5.2 Pre-Treatment Criteria

In order to proceed with day 1 administration of enoxaparin, platelet count must be ≥ 50,000/μl and CrCl must be >/= 50 ml/min. All other laboratory assessments performed within 48 hours of enrollment may be used to determine eligibility and do not need to be repeated.

5.2.1 Cycle 1, Day 1
Enoxaparin syringe will be dispensed by research pharmacy. Baseline assessments for symptoms of VTE or hemorrhage will be recorded. All doses of enoxaparin will be recorded along with time of administration.

5.2.2 Day 7 ± 1 days
Enoxaparin will be ordered on a daily basis and study labs will be continued for those study subjects who remain hospitalized. Assessment for evidence of major hemorrhage or VTE will be recorded by study staff if the participant remains hospitalized.

5.2.3 Day 14 -4, + 7 days
Enoxaparin should be continued until either hospital discharge or day 14. After receiving the final dose of enoxaparin no additional doses of enoxaparin on study will be administered. Assessment for evidence of major hemorrhage or VTE will be recorded. After the day 14 clinical assessment, study staff will become unblinded to treatment allocation in order to appropriately schedule a bilateral lower extremity ultrasound for study subjects on Arm A (see 5.3 below). For participants who remain hospitalized, study subjects should continue with standard pharmacologic thromboprophylaxis per the discretion of the treating physician. Day 14 symptom assessment can be performed by phone.

5.3 Off treatment procedures (unblinding)

Following the completion of the day 14 assessment, study staff will contact a clinical research pharmacist at BIDMC. Criteria for off treatment will be reviewed and then the study staff will be informed as to whether the participant was previously assigned to Arm A (standard enoxaparin) versus Arm B (weight-based enoxaparin). For participants randomized to Arm A, a bilateral ultrasound will be scheduled (see study calendar) to evaluate for asymptomatic deep vein thrombosis.

5.4 Agent Administration

The concentration of enoxaparin is 100 mg/ml. All enoxaparin doses will be diluted to 1 ml final volume such that neither the healthcare providers nor the participant are readily able to identify dosage. Subcutaneous enoxaparin administration may be alternated between the left and right anterolateral and left and right posterolateral abdominal wall once daily.

5.5 General Concomitant Medication and Supportive Care Guidelines

The use of growth factors will be recorded. Subject must be taken off protocol if requires therapeutic anticoagulation or dual antiplatelet agents (eg. aspirin and clopidrogel)

5.6 Criteria for Taking a Participant Off Protocol Therapy

Cessation of enoxaparin and withdrawal from the study is mandated for the following reasons:

- Grade 3 or 4 hemorrhage and/or
  - Symptomatic hemorrhage in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or hemorrhage causing an acute fall in hemoglobin $\geq$ 2g/L or hemorrhage leading to a transfusion of $\geq$ 2 units of packed red blood cells.
- Development of confirmed heparin induced thrombocytopenia
- Proximal deep vein thrombosis or pulmonary embolism
- Condition requiring therapeutic anticoagulation or dual antiplatelet therapy
- Renal failure (see section 6)
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI:

5.7 Duration of Follow Up

Participants will be followed until last scheduled protocol visit. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Participants who have ongoing related adverse events at the last visit will be followed until resolution of those adverse events.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Renal Failure

CrCl (ml/min)	Arm A (standard enoxaparin)	Arm B (adjusted dose enoxaparin)
>40	No change	No change
30-40	No change	**DECREASE to 40 mg daily**
<30	**HOLD**	**HOLD**

Creatinine will be monitored at each study visit and as part of routine medical care. Enoxaparin

will be held for acute renal failure (CrCl <30ml/min) diagnosed at any point during the study.

Enoxaparin should be resumed when CrCl improves to ≥ 40ml/min.

The CrCl can be estimated by either the Modification of Diet in Renal Disease (MDRD) which can be found at http://www.kidney.org/professionals/KLS/gfr_calculator.cfm
or Crockcroft-Gault equation (below)

Men:

$$\text{CrCr (mL/min)} = \frac{(140 - \text{age}) \times \text{body weight [kg]}}{\text{Cr [mg/dL]} \times 72}$$

Women: CrCl (mL/min) = CrCl (as above) * 0.85

Thrombocytopenia

Platelet Count	Arm A (standard enoxaparin)	Arm B (adjusted dose enoxaparin)
≤100,000/µl and ≥50,000/µl (CTCAE Grade 1 or 2)	No change	**DECREASE to 40mg daily**
<50,000/µl (CTCAE Grade 3 or 4)	**HOLD**	**HOLD**

Platelet count will be monitored at least weekly and as part of routine medical care. At any point the platelet count is <50,000/µl, then enoxaparin must be held. Enoxaparin should be resumed at when the platelet count is above 50,000/µl. If heparin induced thrombocytopenia is diagnosed then enoxaparin is to be discontinued.

Hemorrhage

Hemorrhage	**Management/Next Dose for *Arm A (standard enoxaparin)***	**Management/Next Dose for *Arm B (adjusted dose enoxaparin)***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at same dose.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Discontinue (off protocol therapy)	Discontinue (off protocol therapy)
Grade 4	Discontinue (off protocol therapy)	Discontinue (off protocol therapy)
*Participants requiring a delay of >3 days should go off protocol therapy.		

Planned Procedures

Enoxaparin may be held for procedures and should be resumed at the discretion of treating physicians.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Definitions

Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study. All related adverse events will be followed until resolution.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Prolongs inpatient hospitalization (i.e prolonged a hospitalization beyond the expected length of stay).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical

intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for: routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures elective or pre-planned treatment for a pre-existing condition that did not worsen. Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission respite care.

Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list or when it is not included in the informed consent document as a potential risk.

7.2 Expected Toxicities

7.2.1 Adverse Events List for enoxaparin

Enoxaparin can be associated with an increased risk of hemorrhage including life threatening retroperitoneal, gastrointestinal, or intracranial hemorrhages. Cases of epidural or spinal hematomas have been reported with the associated use of enoxaparin and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs. The rate of major bleeding episodes following enoxaparin (40mg daily) in medical patients with severely restricted mobility during

acute illness was <1%.

Thrombocytopenia can occur with the administration of enoxaparin. Moderate thrombocytopenia (platelet counts between 100,000/mm3 and 50,000/mm3) occurred at a rate of 1.3% in patients given enoxaparin, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm3 occurred at a rate of 0.1% in patients given enoxaparin, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials. Thrombocytopenia of any degree should be monitored closely. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with enoxaparin. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow subcutaneous injection of enoxaparin.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.

- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) attributed to heparin (definite, probable or possible) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC as defined below. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	Not required	5 calendar days[b]	24 hours[a]
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours[a]
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
a For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event. b Events that are due to underlying malignancy or its treatment do not need to be reported as SAE					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.5 Reporting to NHLBI

Adverse events and unanticipated problems will be reported by Dr. to NHLBI under the

following timelines:

- Within 7 calendar days of initial receipt of information for fatal of life-threatening unexpected, related serious adverse events.
- Within 15 calendar days of initial receipt of information for non-life threatening unexpected, related SAE
- Within 14 days of the investigator becoming aware of an unanticipated problem that is not an SAE

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **Because of the established toxicity profile of enoxaparin, only attributable AE will need to be recorded. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with enoxaparin administered in this study can be found in Section 7.1.

8.1 *Enoxaparin*

8.1.1 Description

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Maximum anti-Factor Xa and anti-thrombin (anti-Factor Iia) activities occur 3 to 5 hours after subcutaneous injection. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg given subcutaneously, based on anti-Factor Xa activity is approximately 100% in healthy subjects. After repeated subcutaneous administration of 40 mg once daily, the steady state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. Following subcutaneous dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min of enoxaparin. Enoxaparin is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency. Total renal excretion of active and non-active fragments represents 40% of the dose.

8.1.2 **Form**

Enoxaparin is manufactured for subcutaneous injection. Enoxaparin in solution is supplied at varying volumes and concentrations, e.g. 100mg/ml. Enoxaparin is available through various manufacturers and suppliers.

8.1.3 **Storage and Stability**

Recommended storage is 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF)..

8.1.4 **Compatibility –** Normal saline

8.1.5 **Handling**
Care should be taken when handling needles.

8.1.6 **Availability**
Enoxaparin is available from various manufacturers and will be purchased and prepared by the research pharmacy. Enoxaparin will be covered by the grant and provided free of charge.

8.1.7 **Preparation**
The QACT office will inform the research pharmacy of treatment allocation (Arm A or Arm B). The research pharmacy will not be blinded to treatment arm. Appropriate dose of enoxaparin will be aliquoted into syringes and diluted to 1 ml in normal saline. The syringe should not list the enoxaparin dosage.

8.1.8 **Administration**

Participants should be lying down and enoxaparin administered by subcutaneous injection into the abdominal wall on a once daily basis.

8.1.9 **Ordering**
An order will be written and signed by an authorized provider.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**
Any unused study drug will be destroyed on site per standard operating procedures.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

We previously demonstrated the predictive value of circulating tissue factor bearing microparticles in cancer outpatients. We will evaluate if the number of tissue factor bearing microparticles upon hospitalization predicts thrombotic risk. Microparticles will be isolated from plasma by differential centrifugation. We modified an impedance-based flow cytometry system (Beckman Coulter SC Quanta) in order to address the shortcomings of standard light scatter based flow cytometry in the measurement of small (<1 μm) particles.[21] Using this methodology we observed a significant correlation between elevation in tissue factor bearing microparticles and the development of cancer-associated thrombosis.[21, 26]

Based on animal models suggesting that tumor derived tissue factor bearing microparticles accumulate at the site of a developing thrombus through the binding of PSGL-1 with P-selectin, we will evaluate whether subpopulations of TF-bearing microparticles are associated with thrombosis in hospitalized cancer patients. By flow cytometry, we will determine the percentage of TF-bearing microparticles co-expressing the PSGL-1, MUC1, and/or CD14 antigens.

D-dimer is a degradation product of cross-linked fibrin and is the most widely utilized sensitive biomarker to exclude venous thromboembolic events.[27, 28] Utility of D-dimer alone to predict thrombosis in cancer patients is limited due to poor specificity especially using standard cut-offs.[29] D-dimer will be measured by using a commercially available immunoassay (Roche Diagnostics). We will analyze the association between thrombosis and elevated D-dimer values based on standard cutoff of >500ng/L, 75th percentile based on measurements using stored plasma from cancer patients[21, 29] or age adjusted-cutoff which was recently demonstrated to improve assay specificity in a large cohort of patients (including 429 patients with active malignancy).[28] In order not to confound study outcomes, D-Dimer measurements will be performed centrally at BIDMC after the completion of the trial and will not be recorded in the participant's medical record.

9.2 Laboratory Correlative Studies

9.2.1 Microparticles and D-dimer

9.2.1.1 Collection of Specimen:
Blood will be obtained by a non-traumatic venopuncture from peripheral veins or from a central venous catheter draws up to 48 hours prior to the first dose of treatment. A total of 10 ml will be drawn into blue top tubes (3.2% citrate) in either two 5ml tubes or one 15ml tube.

9.2.1.2 Handling of Specimens: First centrifugation should be performed within 1 hour of specimen collection. Plasma separated at 2100 x G for 20 minutes. The plasma layer will be centrifuged a second time at 2100 x G x 20 minutes in a single tube. The plasma supernatant will be transferred to a clean tube leaving the 1ml at the bottom of the tube undisturbed (to be discarded). The transferred plasma sample will be aliquoted (500µl) into 1.5ml eppendorf tubes.

Shipping of Specimens: Tubes can be stored locally at -80ºC and batch sent on dry ice to:

9.2.1.3 Site Performing Correlative Studies: BIDMC

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 48 hours prior to start of protocol therapy.

Event/Procedure	Screening/ Pre-treatment	Day 1	Days 2-6[a]	Day 7[a,c]	Days8-13[a]	Day 14	Day 17
Day Range	-2 to 0			± 1 day		-4, +7 days	± 5 days
Eligibility Assessments	X						
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
ECOG Performance Status Score	X						
Concomitant medication review	X			X		X	
Randomization	X						
Administer enoxaparin		X	X	X	X	X	
Clinical Assessments							
Physical examination including vital signs, and height	X						
Clinical Prediction Score data collection	X						
Weight	X			X			
Assessment of signs and symptoms of VTE and bleeding	X			X		X	
Laboratory Tests							
Plasma storage for correlative studies	X						
Complete blood count	X[d]	X		X			
PT/PTT	X						
Creatinine	X	X		X			
AST/ALT	X						
Imaging							
Bilateral lower extremity ultrasound							X[b]

a: Study subjects will only remain on treatment while hospitalized or until day 14, whichever comes first.
b: Arm A ONLY (standard dose enoxaparin).
c: Day 7 study visit not mandatory if participant is no longer hospitalized.
d: Also record CBC from initial admission

11. MEASUREMENT OF EFFECT

Venous Thromboembolism (VTE)

Cumulative incidence of venous thromboembolic events is the primary endpoint for Arm A and a secondary endpoint for Arm B. ***The composite endpoint includes objectively confirmed proximal or distal lower extremity DVT, subsegmental or larger pulmonary embolism; or fatal PE diagnosed by autopsy***. All other venous or arterial events will be recorded and analyzed as secondary endpoints (including central line associated DVT).

Participants presenting with symptoms compatible with DVT and/or PE will undergo radiographic imaging with compression ultrasound, VQ lung scan, or spiral CT. Confirmed episodes of VTE will be managed by the treating physician per standard of practice.

Presence of any of the following will be considered diagnostic for a VTE:

- New non-compressibility of lower extremity deep venous segments by compression ultrasound.
- Intraluminal defects in two or more views on pulmonary angiography
- Sudden contrast cut-off of one or more vessels greater than 2.5 mm in diameter on a pulmonary angiogram
- A high probability VQ lung scan showing one or more segmental perfusion defects with corresponding normal ventilation (mismatch defect)
- Abnormal spiral CT showing thrombus in pulmonary vessels (subsegmental or larger)

Those VTE that do not qualify for the primary endpoint such as a central line-associated thrombus will be recorded and analyzed as secondary endpoints.

Major Hemorrhage

Adhering to published guidelines, the criteria of major hemorrhage in non-surgical participants is:[30]

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level $\geq$2 g/L or
- Bleeding leading to a transfusion of $\geq$ 2 units of packed red blood cells.

Response Review

VTE: A blinded-centralized independent adjudication of VTE qualifying for the primary outcome will be performed at BIDMC. The review committee will be comprised of two independent radiologists who will review all lower extremity ultrasounds as well as any other imaging that identifies a new thromboembolism. Any disagreements will be settled by consensus.

Major hemorrhage:
An independent adjudication committee of three hematologists will review all details of hemorrhagic events in a blinded manner to determine whether event met criteria for major hemorrhage. Any disagreements will be settled by majority consensus.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method
The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Agreements Language:
N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary aim of randomized phase II trial is to estimate the cumulative incidence of VTE and major hemorrhage in hospitalized cancer patients receiving standard dose or weight adjusted enoxaparin.

13.2 Sample Size, Accrual Rate and Study Duration

The documented incidence of VTE in cancer patients in randomized clinical trials ranges considerably (3-17%) on pharmacologic thromboprophylaxis at standard prophylactic dosing.[8] With the additional incorporation of tumor-specific thrombotic risk assessment, we anticipate the incidence of VTE for high risk cancer patients receiving fixed standard dose enoxaparin will be greater than 10%, especially with inclusion of protocol-mandated lower extremity ultrasounds.

We plan to enroll a total of 50 high risk cancer patients between Beth Israel Deaconess Medical Center and Cleveland Clinic Foundation, of which 25 will be randomized to standard dose enoxaparin. Assuming a cumulative incidence of thrombosis at day 17 is 12% (90% binomial confidence interval 3.3to 28.2%),While we anticipate an increased risk of major hemorrhage observed in cancer patients compared to that of general medical patients, we expect these events to be rate. Point estimates of hemorrhage endpoints at Day 14 will be provided along with the 90% exact binomial confidence intervals. The point estimate will serve to inform sample size calculations for a larger phase III clinical trial.

The trial will only be open at BIDMC and Cleveland Clinic and we anticipate enrolling 3patients per month.

Participants who receive at least one dose of treatment post-randomization will be considered evaluable for the study.

Accrual Targets						
Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
Hispanic or Latino	13	+	12	=	25	
Not Hispanic or Latino	12	+	13	=	25	
Ethnic Category: Total of all subjects	25 (A1)	+	25 (B1)	=	50	(C1)
Racial Category						
American Indian or Alaskan Native		+		=		
Asian	3	+	2	=	5	
Black or African American	5	+	6	=	11	
Native Hawaiian or other Pacific Islander		+		=		
White	17	+	17	=	34	
Racial Category: Total of all subjects	25 (A2)	+	25 (B2)	=	50 (C2)	
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

13.3 Stratification Factors

Randomization will be stratified for hospital (BIDMC and CCF) and risk of cancer based on Khorana model: very high risk (stomach, pancreatic), high risk (lung, lymphoma, gynecologic, bladder, testicular), and standard risk (all others).

13.4 Interim Monitoring Plan

We plan an interim analysis for safety with the DSMBat any point the number of hemorrhages on Arm B is more than 2 greater than observed on Arm A. (We note that the arms are unblinded on day 14, so this plan does not compromise the integrity of the study.) If the true rate of hemorrhage on Arm B is 2%, the probability of observing 2 or more such events in 25 patients is 0.09 In this setting, we will also provide the DSMB with the rates of hemorrhage on Arm A, as this study will provide the best available estimate of the rate of hemorrhage with standard dosing enoxaparin. Efficacy data will also be provided, so that the DSMB can weigh benefit against risk.
There is no plan to adjust the planned enrollment if the event rates are lower than anticipated. The reason being is that the primary goal is evaluate point estimates of VTE and hemorrhage in order to plan for a larger trial rather than adequately power for the direct comparison between fixed dose enoxaparin and intermediate-dose enoxaparin in the current study.

13.5 Analysis of Primary Endpoints

Cumulative incidence of VTE at day 17 (in arm A) and major hemorrhage endpoints at day 14 (both arms) will be calculated along with their 90% exact binomial confidence intervals.

13.6 Analysis of Exploratory Objectives

13.6.1 Efficacy analysis: Although the study is not formally powered to determine efficacy, we will perform a secondary analysis to preliminarily compare the cumulative incidence of symptomatic VTE (data collected prior to unblinding) for the standard dose(Arm A) versus intermediate dose enoxaparin (Arm B). Accordingly, assuming a VTE event rate of 25% which is towards the upper end of the binomial confidence interval in the standard enoxaparin arm compared with a 0% event rate in the intermediate dose enoxaparin arm, the power of the study is 0.74 with a one-sided α of 0.05. The cumulative incidence rate of VTE at day 17 will be estimated using the competing risk method, where VTE is the primary event and death is considered the competing event.[31]

13.6.2 Prediction models: For each of the three scoring systems (Padua, Khorana, IMPROVE), we plan to assess the 2 by 2 contingency table distributions while changing the score cut-offs (such as a Padua score $\geq$6 or an IMPROVE scores $\geq$5 or a Khorana score $\geq$3) in order to evaluate whether the classification probabilities (particularly specificity and sensitivity) change based on the chosen cut-off. The goal is to see if we can determine a more stringent cut-off (compared to a Padua score$\geq$4) by considering the Padua scoring system and/or the other 2 scoring systems to further refine hospitalized cancer patients at high risk of VTE. We aim at maintaining 100% sensitivity, while improving the specificity of the refined risk model. We fully recognize that based on the limited number of patients enrolled that we will have limited power to determine definitively whether the additional risk models can reliably improve specificity without impacting sensitivity. Therefore, we do not plan on utilizing these data to refine the inclusion/exclusion criteria for the planned phase III trial, but rather will confirm the findings within the phase III trial through stratification at time of randomization.

13.6.3 Biomarkers: The primary analysis of each of the biomarkers is to identify whether any of the pre-defined cutoff values are sensitive for VTE in the high risk cancer patients randomized to fixed-dose enoxaparin. Biomarkers such as tissue factor bearing microparticles and D-dimer have previously demonstrated low positive predictive values but high negative predictive values in cancer cohorts.[26, 28, 29] The combination of high tissue factor bearing microparticles ($>3.5x10^4$ microparticles/µl, the top tercile of tissue factor-bearing microparticle concentrations from the reference specimens) and elevated D-dimer further improved the sensitivity and specificity of the individual assays.[26] We will evaluate whether any of the individual biomarkers or combination of biomarkers are sensitive to identify all VTE diagnosed in the high risk cancer patients randomized to fixed-dose enoxaparin. We plan to assess the 2 by 2 contingency table distributions using the pre-defined cut-off values in order to evaluate the classification probabilities (particularly specificity and sensitivity) based on the chosen cut-off. The top tercile of tissue factor-bearing microparticle concentrations and D-dimer or the age-adjusted D-dimer cut-off of the study cohorts will be also considered to evaluate the classification probabilities of the classification model. Fine and Gray univariate regression models will be used to assess the impact of each biomarker classification on the risk of developing VTE. In addition, using regression models we aim at assessing whether there is an association between the scores in the scoring systems and the biomarkers. As this is the initial exploratory evaluation of PSGL-1+ microparticles and thrombosis, additional validation in the phase III trial will be required.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of the first dose of enoxaparin.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All participants will be assessed for primary endpoints as long as received at least 1 dose of enoxaparin following randomization.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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15. APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16. APPENDIX B: SPECIMEN COLLECTION INSTRUCTION AND SHIPPING REPORT

Instructions for Samples collection:

1. **Approximately 10ml of blood** will be drawn into blue top tubes (3.2% citrate) in either two 5ml tubes or one 15ml tube.

2. **First spinning** (centrifugation) should be done within 1 hour of specimen collection. Spin samples at 2100 x G for 20 minutes.

3. Transfer plasma using transfer pipettes to 20cc tube (leave red cell layer undisturbed to be discarded).

4. The plasma supernatant will be transferred to a clean single tube leaving the 1ml at the bottom of the tube undisturbed (to be discarded) and then the plasma layer has to be centrifuged a second time at 2100 x G x 20 minutes.

5. The transferred plasma will be aliquoted into 4-6 cryotubes (up to 500µl per tube) labeled screening visit. Leave the plasma at the bottom of the tube undisturbed (to be discarded).

6. **Label all cryotubes** with the provided pre-filled labels

7. Place tube in biohazard bag and inside an insulated shipper (cooler) with the appropriate quantity of dry ice. Ship sample along with the shipment report form.

Tubes can be stored locally at -80^{o}C and/or batch sent on dry ice to:
Address:

8. Please email study staff at XXX to inform her that samples have been sent.

Specimen Shipment Report

Medical Center: _____

Study ID#: _____

Collection Date: ___/___/____

Time of draw: ☐☐:☐☐ **AM/PM** **Number Samples sent:** _____
Time of spin: ☐☐:☐☐ **AM/PM** **Number Samples store:** _____

Completed By: _____

Comments:

Contact Study Coordinator at Medical Center: _____

Phone: _____ **Email:** _____

This complete form and samples should be mailed to the below address.
Please call or email study staff at BIDMC the day the shipment is sent out.
Thank you!