



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

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A Pilot Trial of Enoxaparin versus Aspirin in Patients with Cancer and Stroke

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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IRB PROTOCOL

IRB#: 12-264 A(11)

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA 4

2.0 OBJECTIVES AND SCIENTIFIC AIMS 4

3.0 BACKGROUND AND RATIONALE 4

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION 5

 4.1 Design..... 5

 4.2 Intervention 5

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS 6

6.0 CRITERIA FOR SUBJECT ELIGIBILITY 6

 6.1 Subject Inclusion Criteria..... 6

 6.2 Subject Exclusion Criteria 7

7.0 RECRUITMENT PLAN 7

8.0 PRETREATMENT EVALUATION 9

9.0 TREATMENT/INTERVENTION PLAN 9

10.0 EVALUATION DURING TREATMENT/INTERVENTION 10

11.0 TOXICITIES/SIDE EFFECTS 11

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT 13

13.0 CRITERIA FOR REMOVAL FROM STUDY 14

14.0 BIostatISTICS 14

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES 15

 15.1 Research Participant Registration 15

 15.2 Randomization 17

16.0 DATA MANAGEMENT ISSUES 17

 16.1 Quality Assurance 20

 16.2 Data and Safety Monitoring 21

17.0 PROTECTION OF HUMAN SUBJECTS 23

 17.1 Privacy 24

 17.2 Serious Adverse Event (SAE) Reporting 24

 17.2.1 25

18.0 INFORMED CONSENT PROCEDURES 26

19.0 REFERENCES 27

20.0 APPENDICES 30



1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase I/II pilot, randomized trial that will compare enoxaparin to aspirin for the prevention of recurrent thromboembolic events in patients with active systemic cancer and acute ischemic stroke. The goal of this study is to determine whether a randomized trial comparing these different antithrombotic strategies in patients with cancer and ischemic stroke is safe and feasible. Patients will be randomized to six months of enoxaparin or aspirin and followed closely for thromboembolic and bleeding events.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary aim: To determine whether a randomized trial comparing enoxaparin to aspirin for the prevention of recurrent thromboembolic events in patients with active systemic cancer and ischemic stroke is feasible. All potentially eligible patients will be rigorously screened for and approached by a study investigator for enrollment. The primary feasibility outcome will be defined as an enrollment rate of $\geq 30\%$ for eligible patients. Secondary feasibility outcomes will be defined as a dropout or crossover rate of $\leq 20\%$ for randomized patients, and adherence to study drug in $\geq 75\%$ of enrolled patients.

Secondary aims: (1) To obtain a preliminary evaluation of the safety of enoxaparin and aspirin in patients with systemic cancer and acute ischemic stroke. The safety endpoints will consist of intracranial hemorrhage, symptomatic intracranial hemorrhage, major bleeding, and death. (2) To obtain preliminary data on the efficacy of enoxaparin and aspirin in patients with cancer and ischemic stroke to enable accurate sample size calculations for a future multi-center trial. Secondary efficacy endpoints will include recurrent ischemic stroke, other thromboembolic events and several functional outcome assessments.

3.0 BACKGROUND AND RATIONALE

Cerebrovascular disease is second only to metastases as a CNS manifestation of cancer (Graus et al 1985). Ischemic strokes, which account for half of these events, frequently arise from unusual stroke mechanisms due to acquired hypercoagulability from the cancer or complications of its therapy (Graus et al 1985; Seok et al 2010; Navi and Segal 2008). Many factors contribute to this prothrombotic state, including secreted procoagulant substances, inflammatory cytokines, increased affinity between tumor cells and blood, endothelial dysfunction, and abnormal protein metabolism (Caine et al 2002). In the largest autopsy-based series to date, the two leading causes of symptomatic ischemic stroke were marantic endocarditis and cerebral intravascular coagulation, both manifestations of hypercoagulability (Graus et al 1985). Based on these histopathologic correlations and few anecdotal case series, some experts and guidelines recommend anticoagulation as the first-line treatment for secondary stroke prevention in patients with cancer and ischemic stroke (Salem et al 2004; Rogers 2010). In addition, many physicians favor heparin over warfarin because of data from small case series and extrapolation from a trial on venous thromboembolic disease (Graus et al 1985; Lee et al 2003).

Conversely, most modern clinical series of patients with systemic cancer and ischemic stroke have not supported a prominent role of hypercoagulability in stroke pathophysiology. In fact, one large observational study found coagulopathy and marantic endocarditis to account for



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

only 12% and 3% of all strokes, respectively (Cestari et al 2004). Another similar study found atherosclerosis to be the most common cause of ischemic stroke in patients with malignancy, and thus proposed antiplatelet agents to be sufficient therapy for most patients with cancer and stroke (Chaturvedi et al 1994). Furthermore, many historic indications for anticoagulation in ischemic stroke in the non-cancer population have not been supported by randomized trials because any reductions in stroke risk were offset by an increased risk of bleeding (Chimowitz et al 2005; Mohr et al 2001). Given the conflicting observational data and the increased risk of bleeding from bone marrow suppression and frequent invasive procedures in patients with cancer, a clinical trial is necessary to determine the optimal secondary stroke prevention regiment (e.g., anticoagulants or antiplatelet agents) for these patients.

Our proposed study would be a significant step in optimizing the management of patients with systemic cancer and acute ischemic stroke because it would determine if a clinical trial comparing anticoagulant (enoxaparin) and antiplatelet therapy (aspirin) in patients with cancer and stroke is feasible, and it would provide a preliminary evaluation of the safety of these different strategies. The former question is particularly germane as patients with cancer may be hesitant to enroll in a secondary stroke prevention trial because of concerns over potential medication interactions and the dynamic nature of oncological care. Once completed, the findings from this study would streamline the methodological planning and sample size calculations for a larger, multi-center trial that would conclusively determine the ideal antithrombotic regiment for these patients. Such a trial would enhance physician practice patterns, ultimately leading to decreased morbidity and improved patient outcomes.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a pilot, randomized, clinical trial comparing enoxaparin to aspirin for the prevention of recurrent ischemic stroke and other thromboembolic events in patients with active systemic cancer.

This study will allow us to determine whether a larger, fully-powered, efficacy trial comparing these different anti-thrombotic strategies in patients with cancer and ischemic stroke would be feasible.

4.2 Intervention

We will recruit 40 adult patients with active systemic cancer who have presented to Memorial Sloan-Kettering Cancer Center (MSKCC), Weill Cornell Medical Center (WCMC) or New York-Presbyterian Hospital (NYPH)/Columbia University Medical Center (CUMC) as an inpatient or outpatient with an acute ischemic stroke within the prior four weeks. Patients will be randomly assigned to receive 6 months of subcutaneous enoxaparin (1 mg/kg BID with a maximum starting dose of 100 mg BID) or 6 months of oral aspirin (81 mg per day unless a higher dose is preferred by study physicians because of a concomitant medical condition, such as coronary artery disease, although the maximum acceptable dose will be 325 mg per day).

Patients who receive anti-thrombotic agents (e.g., enoxaparin, aspirin, clopidogrel, dipyridamole, or warfarin) immediately after stroke onset as part of routine medical care will



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

be eligible for enrollment as long as they can be randomized within 4 weeks of stroke onset and can receive study drug within 1 week of randomization.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Enoxaparin sodium (Lovenox[®]) is a low-molecular weight heparin that is approved by the FDA for the prevention of deep vein thrombosis in abdominal surgery, total hip and knee replacement, and medical patients with immobility during acute illness; the treatment of acute deep vein thrombosis or pulmonary embolism; the prophylaxis of ischemic complications of unstable angina or non-Q-wave myocardial infarction; and the treatment of acute ST-segment elevation myocardial infarction. It is also frequently used “off-label” for the prevention of recurrent stroke and other thromboembolic events in patients with ischemic stroke and hypercoagulable states, including active cancer.

Enoxaparin is manufactured by Sanofi-Aventis U.S., Inc. and is derived from the intestinal mucosa of pigs. It is available as prefilled syringes (30 mg/0.3 ml, 40 mg/0.4 ml), graduated prefilled syringes (60 mg/0.6 ml, 80 mg/0.8 ml, 100 mg/1 ml, 120 mg/0.8 ml, 150 mg/1 ml), or multiple dose vials (300 mg/3.0 ml). It is administered subcutaneously once or twice a day depending on the indication. Commercially available drug will be used for this study.

Aspirin (originally Bayer[®]), also known as acetylsalicylic acid, is an over-the-counter salicylate drug manufactured by numerous pharmaceutical companies, that has an antiplatelet effect by inhibiting the production of thromboxane. It is approved by the FDA for the prevention and treatment of stroke, coronary artery disease, and myocardial infarction, as well as the treatment of rheumatological conditions and pain. It is administered orally or per rectum, and is available in chewable, enteric-coated, immediate-release, and controlled-release forms; available doses include 60, 81, 120, 162, 200, 300, 325, 500, 650, 800, and 975 mg. For this study, subjects will be told to preferentially purchase regular immediate-release 81 mg tabs for oral use. However, other oral formulations (e.g., chewable, enteric-coated, or controlled-release forms) and higher doses up to 325 mg per day will also be allowed. Commercially available drug will be used for this study.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Any adult patient with active systemic cancer diagnosed with acute ischemic stroke at the main MSKCC campus, any of MSKCC’s outpatient centers, WCMC or at NYPH/CUMC, within the prior four weeks would be eligible.

6.1 Subject Inclusion Criteria

- 18 to 85 years of age.
- Active cancer, defined as a pathologic diagnosis of or treatment for any cancer, other than basal-cell or squamous-cell carcinoma of the skin, within the past six months; or patients with known recurrent or metastatic disease within the past six months. A pathology report issued at the enrolling site confirming the diagnosis of cancer is required for study enrollment.
- Acute ischemic stroke within the prior four weeks, defined as a new neurologic deficit(s) with MRI evidence of acute ischemia in a referable location, and no clinical



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

or radiologic indication of a non-cerebrovascular mimic, such as a brain metastasis, as the etiology of the deficit(s).

6.2 Subject Exclusion Criteria

- Inability to get brain MRI
- Known malignant primary brain tumor.
- Diagnosis of intracranial hemorrhage within the past 3 months, including intratumoral hemorrhage into brain metastases from a systemic cancer
- Active or serious bleeding within two weeks of enrollment.
- Patient condition associated with a high risk of bleeding such as recent surgery or peptic ulcer disease.
- Clear indication for anticoagulation (e.g., atrial fibrillation) anticipated during the study period.
- Clear indication for antiplatelet agents (e.g., cardiac stents); a patient receiving aspirin for primary prevention prior to index stroke may be enrolled as long as study investigators believe it would be safe for the patient to stop aspirin if the patient was randomized to the enoxaparin arm.
- Active bleeding diathesis.
- Platelet count of $\leq 70,000/\text{mm}^3$, an international normalized ratio (INR) > 1.6 , or a partial thromboplastin time (PTT) > 40 seconds.
- Known allergy to heparin or aspirin or a history of heparin induced thrombocytopenia.
- Serum creatinine > 2 mg/dl.
- AST or ALT > 200 U/L.
- Hemoglobin < 8 gm/dl
- Symptomatic carotid stenosis.
- Active pregnancy.
- Life expectancy < 1 month or current hospice care
- Unavailability for follow-up.

7.0 RECRUITMENT PLAN

A total of 40 patients will be recruited from the Neurology inpatient and consultation censuses at the main MSKCC campus, MSKCC outpatient centers, WCMC and NYPH/CUMC through screening conducted by research and clinical staff during normal business hours. MSKCC is expected to accrue 6 patients per year, while CUMC and WCMC are each expected to accrue 4 patients per year. All patients enrolled into the trial must sign written informed consent. There are no gender or racial restrictions.

In order to satisfy all of the study's feasibility endpoints, MSKCC, WCMC and NYPH/CUMC staff will screen all ischemic stroke patients and will systematically record the total number of patients with ischemic stroke, the total number with ischemic stroke and active systemic cancer, the total number that are eligible for the trial (and if not eligible the reason(s) why), the total number approached for enrollment, and the total number enrolled.

Patients who drop out of the study before the 3-month timepoint for reasons other than a safety or efficacy event or death will be replaced.

Potential research subjects will be identified by a member of the patient's treatment team, a protocol investigator, or research team. If the investigator is a member of the treatment team,



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

he or she will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigators may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator, or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

This limited waiver will apply only to MSKCC. Any participating sites that require a limited waiver must obtain it from their own local IRB/Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the MSKCC staff to confirm the participating data collection site(s) have a limited waiver approved by their local IRB(s)/PBs.

8.0 PRETREATMENT EVALUATION

The following studies are required within four weeks of registration, all of which are routinely performed as part of standard practice in patients with active cancer and acute stroke:

- Complete history and physical exam including neurological exam.
- Modified Rankin Scale.
- NIH Stroke Scale.
- Karnofsky Performance Status Scale.
- Height and weight.
- CBC including WBC differential and platelet count.
- Coagulation studies, including PT, PTT, and INR.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

- Serum D-Dimer and fibrinogen level.
- Comprehensive chemistry panel (see appendix F).
- Electrocardiogram (EKG).
- Carotid artery imaging with MRA, CTA, or ultrasound.
- MRI scan of the brain (contrast is not required).

The complete history and physical examination, height and weight, CBC, coagulation studies, comprehensive chemistry panel (see appendix F), EKG, carotid artery imaging, and MRI of the brain must be performed before registration, while the other required studies may be performed after registration as long as they are done within two weeks after the date of registration.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Subcutaneous Enoxaparin

Half the study patients (n=20) will be randomized to subcutaneous enoxaparin. This medicine will be injected twice daily at a dose of 1 mg/kg with a maximum starting dose of 100 mg BID. Patients who weigh more than 100 kg will start at a dose of 100 mg BID; their subsequent dosing will be guided by hematology and may change. Treatment is routine, and should begin within 7 days of randomization (either inpatient or outpatient) and continue for 6 months. A registered nurse will teach patients randomized to the enoxaparin arm how to perform subcutaneous injections; in cases of significant patient handicap, a surrogate of the patient will be taught to perform the injections.

9.2 Oral Aspirin

The other half of study patients (n=20) will be randomized to oral aspirin. The medicine will be administered daily at a dose of 81 mg unless a concomitant medical condition, such as coronary artery disease, dictates a higher dose of aspirin to be administered instead (maximum dose 325 mg daily). Treatment is routine, and should begin within 7 days of randomization (either inpatient or outpatient) and continue for 6 months.

9.3 Medications to Avoid

The following medications should be avoided during the course of the study in order to reduce the risk of bleeding side effects: clopidogrel (Plavix®), prasugrel (Effient®), ticlopidine (Ticlid®), cilostazol (Pletal®), dipyridamole (Persantine®, Aggrenox®), ticagrelor (Brilinta®), abciximab (Reopro®), antithrombin (Atryn®), antithrombin III (Thrombate III®), argatroban (Argatroban®), dabigatran (Pradaxa®), dalteparin (Fragmin®), danaparoid (Orgaran®), Desirudin (Iprivask®), fondaparinux (Arixtra®), lepirudin (Refludan®), tinzaparin (Innohep®), warfarin (Coumadin®), rivaroxaban (Xarelto®), apixaban (Eliquis®), urokinase (Abbokinase®, Kinlytic®), reteplase (Retavase®), and tenecteplase (TNKase®),

Alteplase (Activase®) should also be avoided in patients randomized to the enoxaparin arm; however, patients randomized to the aspirin arm who develop an acute ischemic stroke could receive alteplase for thrombolysis if they fulfill all standard eligibility criteria.



10.0 EVALUATION DURING TREATMENT/INTERVENTION

Routine blood tests consisting of CBC, comprehensive metabolic panel (see appendix F), PT, PTT, INR, D-Dimer, and fibrinogen will be performed at 2 weeks (+/- 4 days) and 1 month (+/- 4 days) after treatment initiation for safety and efficacy purposes in accordance with standard clinical practice.

Patients will be evaluated by a study investigator at 1 month (+/- 1 week), 3 months (+/- 1 week), and 6 months (+/- 1 week) after treatment initiation by clinical visit, which can occur at MSKCC's main hospital and Basking Ridge, Commack and West Harrison regional network sites, WCMC, and NYPH/CUMC. The clinical visit will consist of history taking and physical examination, and will assess for adherence to study drug (using the 8-point Morisky medication adherence scale) and any symptoms or signs of clinical thromboembolism, bleeding episodes, or serious adverse events. The study investigator will also assess functional outcomes by performing a modified Rankin Scale (mRS), a National Institute of Health Stroke Scale (NIHSS), and a Karnofsky Performance Status Scale (KPSS). Investigators administering the mRS and NIHSS will be certified to do so. If patients are unavailable for an in-person follow-up or their medical condition prohibits them from participating, then the patient or their surrogate will be interviewed instead by phone by one of the study investigators for outcome measures. Telephone interviews will consist of the same assessments as the clinical visit except that there will be no physical examination or NIHSS, as these interventions can only be performed in person.

The 8-point Morisky medication adherence scale (MMAS) is a validated and reliable drug adherence scale that is commonly used to monitor adherence over the course of a treatment (see appendix A) (Morisky et al 2008). The scale consists of eight questions on medication-taking behavior and was originally developed to evaluate patient adherence to blood pressure medicines but has been effectively used for numerous chronic disorders. Response choices are yes/no for items 1 through 7, while item 8 consists of a 5-point Likert scale. For items 1 through 7, each response "no" equals 1 point and each response "yes" equals 0 points, except for item 5, in which a "yes" response equals 1 point and a "no" response equals 0 points. For item 8, if a patient chooses response "0", they receive 1 point, while responses "1", "2", "3", and "4" equate to 0.75, 0.5, 0.25, and 0 points, respectively. The MMAS will be completed by patients at all scheduled clinical visits (1, 3, and 6 months) and study drug adherence will be defined as a mean total score of ≥ 6 as previous studies have demonstrated this cutpoint to effectively differentiate between low and medium or high adherence.

The mRS is a validated and widely used neurological disability scale that measures patients' ability to perform activities of daily living. The score ranges from 0 to 6, with 0 indicating no symptoms and 6 representing death (see appendix B). Patients' scores will be calculated by a study investigator shortly after the interview with the assistance of a structured questionnaire (for reference only). All study investigators performing the mRS will have completed an instructional course and be certified in calculating the score prior to the start of the project. The score's strengths are its simplicity, reliability, and easy applicability.

The NIHSS is a validated and commonly used stroke severity scale, ranging from 0 (normal exam) to 42 (coma and quadriplegia) (Brott et al 1989; Goldstein et al 1997). It involves a



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

bedside neurological examination that assesses multiple components of patients' neurological function including level of consciousness, speech and language, eye movements, visual fields, motor strength, sensory function, and coordination of limbs (see appendix D). The test takes approximately 10 minutes to complete—5 minutes to administer and another 5 minutes to record the scores properly. All study investigators performing the NIHSS will have completed an instructional course and be certified in calculating the scale prior to study initiation. The scale will be used to determine patients' level of impairment before and after treatment with the study drugs.

The KPSS is a reliable and commonly used performance scale that quantifies cancer patients' functional status (Karnofsky and Burchenal 1949; Ma et al 2010). The score is often used by oncologists to assess cancer patients' eligibility for clinical trials, estimate prognosis, and predict toxicity and likelihood of response to therapy. The score ranges from 100 to 0, where 100 is normal with no signs of disease or patient complaints and 0 is death (see appendix E). Patients' scores will be calculated by a study investigator shortly after the neurologic examination that will evaluate patients' activity level and need for assistance. All study investigators performing the score will work primarily in a cancer hospital and will be familiar with the score and its calculation.

Patients randomized to the aspirin arm who require deep vein thrombosis prevention during the study may concomitantly receive *prophylactic doses* of heparin or other anticoagulants, if necessary. However, if patients develops a new indication for treatment dose anticoagulation within 6 months of study drug initiation, they will be removed from study drug, and further anti-thrombotic therapy, if any, will be dictated by their treating physicians. These patients will, however, continue to be followed by study investigators to one-year for survival and safety/efficacy outcomes via electronic medical records.

At 6 months, patients will have completed their randomized study treatment. Any subsequent anti-thrombotic therapy will be dictated by their treating physicians and can include enoxaparin, aspirin, or another medicine. However, patients will continue to be followed by study investigators to one-year for survival and safety/efficacy outcomes via electronic medical records.

Additionally, if patients develop a safety or efficacy outcome of interest within 6 months of treatment initiation, they will be removed from study drug, and further anti-thrombotic therapy, if any, will be dictated by their treating physicians. However, these patients will also continue to be followed by study investigators to one-year for survival and other outcomes via scheduled visits at 1, 3, and 6 months and electronic medical records from 6 months to 1 year.

11.0 TOXICITIES/SIDE EFFECTS

The greatest risk to patients is hemorrhage from study drugs, particularly the low molecular weight heparin enoxaparin. This medication has never been systematically assessed in cancer patients with acute stroke, so rates of major hemorrhage must be estimated from studies of patients with cancer or stroke in isolation.

The low molecular weight heparin, dalteparin, was associated with a 6% 6-month rate of major bleeding but only one case (0.3% of cohort) of intracranial hemorrhage in a large



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

randomized trial of patients with cancer and deep vein thrombosis (Lee et al 2003). Low molecular weight heparin has also been associated with a slightly increased risk of major hemorrhage in stroke trials performed in the general population (Bath et al 2001; TOAST investigators 1998). However, cancer patients are intrinsically hypercoagulable, so a small excess risk of major hemorrhage may be outweighed by reduced rates of thromboembolism. Furthermore, despite little supportive data, anticoagulation is routinely used for the treatment of ischemic stroke in patients with cancer, highlighting the need for a trial to assess the safety and feasibility of this practice.

Aspirin use is also associated with a small increased risk of systemic and intracranial hemorrhage (1-2% overall rate of major bleeding, mostly due to gastrointestinal hemorrhages); however, its cardiovascular benefits clearly outweigh these risks (CAST Collaborative group 1997; IST Collaborative group 1997).

If intracranial hemorrhage or major bleeding occurs (see definitions in section 12.0), the patient's study drug (enoxaparin or aspirin) will be discontinued, and the patient will be referred for emergency medical evaluation. Furthermore, dose modifications will not be allowed for participants experiencing these major side effects while in this study. Therefore, any unacceptable toxicity reported by a participant will be considered reason for removal from the study, unless otherwise indicated by the MSKCC principal and/or co-principal investigator.

In the event of minor bleeding or other minor adverse events, the study drug can be held temporarily at the discretion of the treating physician. In such circumstances, the study drug should be restarted at a later time point when deemed appropriate by the treating physician. Adverse events will be graded using version 4.0 of the NCI Common Terminology Criteria for Adverse Events.

Other potential risks to patients from study drugs include:

Enoxaparin

- <10%: injection site ecchymosis and hematoma, easy bleeding from minor cuts or wounds, elevated liver enzymes.
- <5%: anemia, nausea or vomiting, diarrhea, thrombocytopenia.
- <1%: allergic reaction, heparin-induced thrombocytopenia.

Aspirin

- <10%: easy bleeding from minor cuts or wounds.
- <5%: dyspepsia, nausea or vomiting, dizziness.
- <1%: allergic reaction, renal dysfunction, hearing loss or tinnitus.

If a patient is discovered at any time to have a platelet count < 70,000/mm³, hemoglobin < 7 gm/dl, PTT > 80 seconds, INR > 3, or creatinine > 2.5 mg/dl because of chemotherapy or other medical reasons, then the patient's study drug will be temporarily discontinued and weekly, relevant blood tests will be performed. The study drug will only be reinstated if the abnormal laboratory values return to acceptable levels as deemed by the principal and/or co-principal investigator. Treating physicians will also be encouraged to contact study



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

investigators whenever there is concern for a heightened bleeding risk, so that more vigilant monitoring is performed.

To ensure that the study medications are not excessively increasing the rates of serious adverse events, an external data and safety monitoring board as detailed in Section 16.2 will periodically review all potential adverse events and will have the authority to stop further enrollment into the study if unacceptable rates of hemorrhage or death are discovered.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Primary safety and secondary efficacy outcomes will be assessed for by a study investigator at 1 month (+/- 1 week), 3 months (+/- 1 week), and 6 months (+/- 1 week) after initiation of treatment by interviewing the patient and/or surrogate via an in-person visit or phone conversation and by reviewing any relevant medical records. The occurrence of an outcome will be dichotomized as yes or no, although a single patient may have multiple outcomes. The outcomes of interest are defined as follows:

Safety Outcomes

Intracranial Hemorrhage: Acute extravasation of blood into the brain parenchyma, subarachnoid space, subdural space, or epidural space as demonstrated by neuroimaging, surgical exploration, or autopsy.

Symptomatic Intracranial Hemorrhage: Intracranial bleeding associated with any clinical deterioration or associated with death.

Major Bleeding: Bleeding associated with death; any intracranial hemorrhage; or a systemic hemorrhage requiring hospitalization, blood transfusion, or surgery.

Efficacy Outcomes

Ischemic Stroke: New neurologic deficit(s) with CT or MRI evidence of acute ischemia in a referable location, and no clinical or radiologic indication of a non-cerebrovascular mimic as the etiology of the deficit(s).

Transient Ischemic Attack: Transient neurologic deficit lasting less than 24 hours, attributed to focal brain ischemia without evidence for another etiology or cerebral infarction on CT or MRI.

Myocardial Infarction: Any combination of two of the following three criteria: chest pain, elevated cardiac enzymes (as per specific laboratory guidelines), or dynamic ECG changes consistent with ischemia.

Deep Vein Thrombosis: Thrombosis of the deep venous circulation diagnosed via Doppler examination, magnetic resonance venography, or spiral CT.

Pulmonary Embolus: Thrombosis of the pulmonary circulation diagnosed by spiral CT of the chest or V/Q scan.

Systemic Arterial Thrombosis: An acute vascular occlusion of an extremity or organ,



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

documented by means of imaging, surgery, or autopsy.

Though our primary objective is to assess the safety and feasibility of the interventions, we will also assess functional outcomes at approximately 1 month, 3 months, and 6 months after initiation of treatment using the mRS score, NIHSS, and KPSS.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at anytime the patient develops unacceptable toxicity such as major bleeding, intracranial hemorrhage, or a severe allergic reaction, he or she will be removed from the study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

If at anytime the patient withdraws consent for continued participation or dies, he or she will be removed from the study.

14.0 BIOSTATISTICS

Patients will be randomized at registration to receive 6 months of subcutaneous enoxaparin or 6 months of oral aspirin. Please see section 15.2 for details about this process.

The enrollment rate will be the proportion of eligible patients who enroll in the study. The study will be considered feasible if the lower bound of the 95% confidence interval (CI) of the enrollment rate exceeds 30%. Therefore, our feasibility criterion will be met if 40 of the first 100 (40%; 95% CI, 30.3-50.3%) screened and eligible patients enroll. However, even if our feasibility criterion is not met, we will continue to target up to another 50 patients (for a total of 150 targeted patients) in an attempt to enroll 40 patients and thus obtain sufficient preliminary data on safety outcomes. Assuming at least a 30% recruitment rate in eligible patients and a 10% dropout rate among randomized patients, and given that MSKCC, WCMC and CUMC care for approximately 280 total patients with cancer and recent stroke per year, and roughly 15% of these patients would be eligible for this trial (based on 2015 data and the current eligibility criteria), we anticipate a total enrollment period of 5 years for our pre-planned sample size of 40 patients. Therefore, since the trial started January 2013, we anticipate that it will be completed by July 2018.

Because this is a pilot trial, the main aim of the study will be to assess the feasibility of enrollment and randomization and the safety of the intervention regimens. However, several secondary efficacy outcomes will also be assessed to enable accurate sample size calculations for a future, larger, multi-center trial that will be sufficiently powered to detect clinically relevant differences in efficacy outcomes. All outcomes will be assessed for occurrence approximately at 1 month, 3 months, and 6 months after initiation of the study drug, and are defined in detail in the Criteria for Therapeutic Response/Outcome Assessment section.

The primary feasibility outcome will be the enrollment rate among eligible patients (i.e., screened patients that fulfill all subject inclusion and exclusion criterion regardless of whether they are approached for enrollment by a study investigator); our target enrollment rate is



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

≥30%. Patients who enroll into the study but then dropout or crossover will still be considered successfully enrolled.

Secondary feasibility outcomes will be the dropout or crossover rate among randomized patients and the study drug adherence rate among enrolled patients; the target dropout or crossover rate is ≤20% and the target adherence rate is ≥75%. Study drug adherence is considered a dichotomous variable for individual patients in this study and will be determined by the 8-point MMAS. Patients whose mean total MMAS score is ≥6 will be considered adherent. As noted in section 7.0, patients who drop out of the study before the 3-month timepoint for reasons other than a safety or efficacy event or death will be replaced.

The primary safety outcomes will consist of intracranial hemorrhage, symptomatic intracranial hemorrhage, major bleeding, and death. Because the study's target sample size is small and our secondary aim is to only obtain preliminary data on the safety of study drugs (not to perform formal analysis of safety data), there will be no pre-specified stopping rule for this study. However, an external MSKCC data and safety monitoring board will periodically review all potential adverse events and will have the authority to stop further enrollment based on any safety concerns.

Secondary efficacy outcomes will include: recurrent ischemic stroke; all strokes (ischemic or hemorrhagic); a thromboembolic event composite consisting of recurrent ischemic stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis, pulmonary embolism, or systemic arterial thrombosis; the modified Rankin Scale at 1, 3 and 6 months (van Swieten et al 1988); the National Institute of Health Stroke Scale at 1, 3 and 6 months (Brott et al 1989); and the Karnofsky Performance Status Scale at 1, 3 and 6 months.

Descriptive statistics will be used to characterize the rates of eligibility, recruitment, randomization, dropout, and adherence. The chi-square test will be used to compare the rates of safety and efficacy outcomes between groups for dichotomous variables, and analysis of covariance (ANCOVA) will be used to evaluate differences in continuous variables over time accounting for pre-treatment values. Our primary analysis will use the intention-to-treat principle, but we will also perform a secondary as-treated analysis. Therefore, for our primary (intention-to-treat) analysis, outcomes will be analyzed according to patients' randomized study drug, regardless of prior anti-thrombotic use in the period between stroke onset and study drug initiation or the duration of study drug.

Since this is a pilot trial primarily intended to assess safety and feasibility, we will be underpowered to detect any significant differences between groups for our secondary efficacy outcomes. However, this pilot trial will enable us to better estimate event rates in our population, and thus more accurately perform sample size calculations in the future for a fully-powered trial.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section 6.0, entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section 18.0, entitled Informed



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

Consent Procedures.

During the registration process, registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (<http://ppr/>). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 For Participating Sites

Central registration for this study will take place at MSKCC.

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax or email the registration/eligibility documents to:

Benjamin Weill
Fax: (646) 227-7243
Email: weillb@mskcc.org

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at MSKCC will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, the participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC PPR Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.



15.2 Randomization

After eligibility is established and consent is obtained, patients will be registered by MSKCC in the PPR system and randomized using the CRDB. The treatment group to which the participant was assigned to will be available right after registration, by calling the MSKCC PPR registry between the hours of 8:30 AM and 5:30 PM, Monday through Friday, or by login in the Clinical Research Database Web Client (CRDBi); randomization of eligible patients will only occur during these times. Randomization codes will be generated in the CRDB.

Since patients with adenocarcinomas may be intrinsically more hypercoagulable than patients with other tumor types (Seok et al 2010), stratified blocked randomization will be undertaken to ensure similar numbers of patients with these carcinomas in each group.

Participating sites will receive a formal notification about the randomization status as soon as this becomes available.

16.0 DATA MANAGEMENT ISSUES

A MSKCC Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, data abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of activities amongst the protocol study team.

All collected data will be entered into a secure, password-encrypted database at MSKCC (CRDB), which only key study personnel will have access to. Source documentation will be available to support the computerized patient record.

16.0.1. Data and Source Documentation for Participating Sites

Data

The participating site(s) will enter data remotely into MSKCC's internet-based Clinical Research Database, termed CRDBi-Multicenter. Standardized Case Report Forms (eCRFS) and data entry guidelines have been generated for this study. The site staff will receive CRDB training prior to enrolling its first patient. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A schedule of required forms is shown in the table below. Participating sites will be responsible for completing eCRFs and submitting them to MSKCC per the designated timelines.

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline MRI that confirms evidence of acute ischemic stroke
- A pathology report issued in the enrolling site confirming this diagnosis is required for study enrollment.
- Treatment records
- Required protocol assessment documents
- Grade 3-5 toxicities/adverse events

Source documentation should include a minimum of two identifiers to allow for data



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into CRDBi-Multicenter and study-specific eCRFs. Source documentation should be sent to MSKCC at the contact provided below. Submissions should include a cover page listing all source documentation enclosed per participant.

Department of Neurology Clinical Research Team
Attn: Benjamin Weill, RSA
633 3rd Avenue, 12th Floor
New York, NY 10017
weillb@mskcc.org
Phone: 646-227-2610
Fax: 646-227-2461

Participating sites are required to keep copies of each form that is sent via postal mail.

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to the following chart:



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

Data and Source Submission Requirements and Timelines for Therapeutic Studies

	Baseline	Treatment start	Treatment day 15	1 month visit	3 month visit	6 month visit/Off treatment	Serious Adverse Events	Survival Follow up/Off study
Submission Schedule								
Source documentation	Within 24 hours (see section 15.1.1)	within 14 days of visit					Within 3 days of event (see section 17.2.1); updates to be submitted as available	within 14 days of visit
eCRF	Within 7 days of registration							
Required Forms								
Minimal Dataset: Patient Information	X							
Minimal Dataset: Initial Disease Info	X							
Minimal Dataset: Disease Status	X							X
Minimal Dataset: Histology	X							
Minimal Dataset: Outcome Info				X	X	X		
Minimal Dataset: Patient Status	X	X	X	X	X	X		X
General Forms: Comorbidity	X			X	X	X	X	
General Forms: Concomitant Drug	X			X	X	X		X
General Forms: Diagnostic Test	X							
General Forms: Laboratory	X		X	X				
General Forms: Pathology	X							
General Forms: Physical Exam	X			X	X	X		X
General Forms: Prior Therapy	X							
General Forms: Toxicity	X			X	X	X	X	X
General Forms: Treatment	X			X	X	X		X
General Forms: Hospitalization	X						X	X
General Forms: Serious Adverse Event							X	



Off-Study Requirements

When a patient is taken off-study, any outstanding data and required source documentation are required to be sent to MSKCC no later than 14 calendar days after the off-study date. Failure to submit required forms in the timelines requested may result in suspension of accrual privileges at a given site until data is updated, and/or withholding of contract payments if applicable.

The MSKCC PI may request from outside sites imaging documenting any PR or CR.

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be created to assess for any missing or inconsistent data. In addition, accrual rates and the extent and accuracy of outcome assessments and follow-up will be monitored periodically throughout the study period, and any potential issues will be immediately brought to the attention of the study team for discussion and rectification, if necessary.

The study team will also perform random-sample data quality and protocol compliance audits at least two times per year to ensure the integrity of the data.

16.1.1 Quality Assurance for Participating Sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing

- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Case Report Form submissions to MSKCC: timeliness and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf>

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality, including several institutional and departmental processes. For instance, at the institutional level, there is protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA. Additionally, there are two institutional committees—the Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials—that are responsible for monitoring the activities of our clinical trials program and report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, industry sponsored, NCI cooperative group, etc...) will be addressed and the monitoring



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at each participating site.
- Participating site laboratory certifications and reference ranges

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years.

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

This study intends to obtain more in-depth information about the safety and feasibility of two commercially available drugs, enoxaparin and aspirin, in cancer patients with acute ischemic stroke. The findings of the proposed pilot study will enable the planning and development of a larger, fully-powered clinical trial that will assess for efficacy.

The potential risks for participants in this study are easy bruising, skin irritation, pain at the injection site, dyspepsia, dizziness, diarrhea, nausea and vomiting, hearing loss, tinnitus, impaired liver function, thrombocytopenia, anemia, major bleeding, intracranial hemorrhage, and allergic reactions. Participants who experience major adverse events (e.g., major bleeding, intracranial hemorrhage, severe allergic reactions) caused by the study treatments will be readily removed from the study.

All research specific assessments proposed for this study are also used for the assessment of non-protocol patients; the burden caused to patients by them is minimal.

This protocol will not include children because most pediatric cancers are hematologic in origin and may not induce as much hypercoagulability as the more common carcinomas of adulthood (Rogers 2012). Furthermore, strokes are extremely rare events in children.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org.

A serious adverse event is any adverse events that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The CRDB SAE report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

MSKCC)

- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - An explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains in the study
 - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgements must be sent to MSK upon receipt.
- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Form found in MSKCC's internet-based Clinical Research Database, CRDBi-Multicenter, to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:

PI:
Lisa M. DeAngelis, MD
1275 York Avenue
New York, NY 10065
Tel 212-639-7523
Fax 212-717-3296

Co-PI:
Babak Navi, MD
353 E 68th Street
New York, NY 10065



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

Tel 212-639-7123

Research Study Assistant I:
Benjamin Weill
Department of Neurology
Memorial Sloan-Kettering Cancer Center
160 E 53rd Street, 2nd Floor
New York, NY 10022
Tel: 212.610.0348
Fax: 646.227.2461
Email weillb@mskcc.org

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2.1
- The MSKCC PI is responsible for informing all participating sites about all deaths and unexpected SAEs that are possibly, probably, or definitely related to the study drug within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.3 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit outside safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 12-264 A(11)

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

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MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 12-264 A(11)

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MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

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20.0 APPENDICES

Appendix A: 8-point Morisky questionnaire

Appendix B: Modified Rankin Scale.

Appendix D: National Institute of Health Stroke Scale.

Appendix E: Karnofsky Performance Status Scale.

Appendix F: Comprehensive Metabolic Panel