

Study Protocol

Official Title: Extended Prophylactic Anticoagulation Following Spinal Surgery for Metastatic Disease

ClinicalTrials.gov ID (NCT number): Pending

Protocol Date: 7/13/2026

CLINICAL TRIAL PROTOCOL

Extended Prophylactic Anticoagulation Following Spinal Surgery for Metastatic Disease

Protocol Version 1.2 Date: July 13, 2026

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STUDY SPONSOR: Beckwith Institute Frontline Innovation Program

STUDY SITES: UPMC Presbyterian Hospital, UPMC Shadyside Hospital, UPMC Mercy Hospital

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1. PROTOCOL SYNOPSIS

Title: Extended Prophylactic Anticoagulation Following Spinal Surgery for Metastatic Disease

Short Title: Extended Postoperative Anticoagulation for Spine Mets

Phase: Pilot/Feasibility Study

Study Design: Single-arm, prospective, open-label interventional drug study with historical controls

Primary Objective: To determine if extended prophylactic anticoagulation with apixaban 2.5 mg twice daily for 30 days following hospital discharge is safe and effective for the prevention of venous thromboembolism (VTE) in patients who have undergone spinal surgery for metastatic disease.

Study Population: Adult patients (≥ 18 years) who have undergone spinal surgery for vertebral metastatic disease at UPMC Presbyterian, Shadyside, or Mercy hospitals.
Sample Size: 50 patients (prospective cohort) compared to 68 patients (historical control cohort)

Intervention: Apixaban 2.5 mg orally twice daily for 30 days following hospital discharge

Primary Endpoint: Incidence of symptomatic venous thromboembolism (deep vein thrombosis or pulmonary embolism) within 90 days of hospital discharge

Secondary Endpoints:

- Major bleeding events within 90 days of discharge
- Clinically relevant non-major bleeding events within 90 days of discharge
- All-cause mortality at 90 days
- Medication adherence (pill count at Day 31)

Study Duration:

- Enrollment period: 12 months
- Subject participation: 91 days from discharge
- Total study duration: Approximately 16 months

Study Sites: UPMC Presbyterian, UPMC Shadyside, UPMC Mercy

Principal Investigator: James Bayley, MD

Sponsor: Beckwith Institute Frontline Innovation Program

IND Status: IND exemption per 21 CFR 312.2(b)(1). Apixaban is an FDA-approved drug being evaluated for an off-label indication (VTE prophylaxis following spinal surgery for metastatic disease). The study does not involve a new route of administration or dose level. The proposed dose (2.5 mg BID) is identical to the FDA-approved prophylactic dose following hip and knee arthroplasty. The patient population is at comparable or greater VTE risk than the approved arthroplasty indication, and all subjects will have demonstrated tolerance of inpatient anticoagulation prior to enrollment. The study is not intended to support a new indication, labeling change, or advertising change for apixaban. IND exemption documentation on file.

ClinicalTrials.gov Registration: [To be completed prior to first enrollment]

2. SCHEMA

STUDY DESIGN SCHEMA

Pre-Screening: - Review OR schedule to identify patients undergoing spine surgery for metastatic disease - Medical record review under waiver of consent to assess eligibility

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Enrollment (Day of Hospital Discharge): - Informed consent obtained - Baseline data collection - Apixaban dispensed by Investigational Drug Service and delivered to the subject by study team) - Patient education on bleeding signs/symptoms



Day 1 Post-Discharge: - Patient begins apixaban 2.5 mg orally twice daily



Day 2 Post-Discharge: - Telephone follow-up - Assess medication initiation, early adverse events - Assess bleeding symptoms



Days 3-30: - Patient continues apixaban 2.5 mg BID - Patient contacts study team for any adverse events



Day 31 Post-Discharge: - Telephone follow-up - Assess VTE symptoms, bleeding events - Medication adherence assessment (pill count) - Healthcare utilization assessment



Days 32-90: - Observation period (no study drug) - Medical record review for VTE, bleeding, mortality



Day 91 Post-Discharge: - Final telephone follow-up - Assess VTE events, bleeding events, mortality - Healthcare utilization assessment - Study completion



PRIMARY ANALYSIS: Compare VTE rates (prospective cohort vs. historical controls) Compare bleeding rates (prospective cohort vs. historical controls) Bayesian analysis of probability of benefit

3. BACKGROUND AND RATIONALE

3.1 Background

3.1.1 Venous Thromboembolism After Cancer Surgery

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality in patients undergoing surgery for cancer. Data from the @RISTOS project, a prospective multicenter observational study of over 2,300 patients undergoing general, urologic, and gynecologic cancer surgery, demonstrated that VTE is the most common cause of death at 30 days after surgery, with approximately 40% of clinically overt VTE events occurring more than 21 days postoperatively.[1] These findings established the biological rationale for extended VTE prophylaxis beyond the immediate perioperative period in high-risk cancer surgery patients.

Current guidelines from the American Society of Clinical Oncology (ASCO) recommend extended pharmacologic VTE prophylaxis (continuing for 4 weeks after surgery) for patients undergoing major abdominal or pelvic cancer surgery.[2] The American College of Chest Physicians (ACCP) similarly endorses extended thromboprophylaxis for high-risk surgical oncology patients.[8] The clinical trial evidence supporting these recommendations includes the ENOXACAN II trial, which demonstrated that 4 weeks of enoxaparin following major abdominal cancer surgery significantly reduced VTE

compared to 1 week of prophylaxis (4.8% vs 12.0%, $p=0.02$) without a significant increase in major bleeding.[6] The postoperative period during which VTE risk remains elevated extends considerably beyond the inpatient stay, particularly in oncologic patients: a large prospective cohort study by Sweetland et al. reported that VTE risk remained elevated for up to 12 weeks following major surgery.[7] These data collectively underscore the inadequacy of prophylaxis limited to the hospitalization period alone.

3.1.2 VTE Risk in Spinal Surgery for Metastatic Disease

Patients undergoing spinal surgery for metastatic disease face a uniquely elevated VTE risk driven by the convergence of malignancy-associated hypercoagulability, the thrombogenic nature of spinal surgery, and the immobility that commonly accompanies both the disease and its treatment. Groot et al. conducted the largest retrospective study to date specifically examining symptomatic VTE following surgery for spine metastatic bone lesions ($N=637$), reporting a 90-day symptomatic VTE rate of approximately 11%. Importantly, this risk increased substantially beyond the immediate postoperative period, with a notable rise in events after 30 days — precisely when standard inpatient prophylaxis has ended. Patients who developed symptomatic VTE had significantly worse 1-year survival compared to those who did not (38% vs 47%, $p=0.044$).[3]

De la Garza Ramos et al. examined the timing of pharmacologic anticoagulation initiation following surgery for spinal metastatic tumors and found that earlier initiation was associated with lower rates of pulmonary embolism without a significant increase in wound complications, though extended outpatient prophylaxis was not evaluated.[4] A systematic meta-analysis by Zhang et al. identified malignancy, prolonged operative time, advanced age, preoperative neurological deficit, and posterior surgical approach as independent risk factors for VTE following spinal surgery, further characterizing this population's vulnerability.[5]

At our institution, a retrospective analysis of 68 consecutive patients who underwent surgery for spinal metastatic disease at UPMC Presbyterian and UPMC Shadyside hospitals between January 2022 and December 2024 identified a 90-day VTE rate of 14.7% (10/68), consistent with the published literature and confirming the high burden of this complication in our local population. The 90-day all-cause mortality was 16% (11/68), none of which were adjudicated as directly related to VTE.

3.1.3 Current Standard of Care and the Evidence Gap

Despite the well-documented high VTE risk in patients undergoing surgery for spinal metastatic disease, there are currently no established guidelines for extended outpatient VTE prophylaxis in this population. Standard practice at most centers, including our own, consists of inpatient pharmacologic prophylaxis (typically subcutaneous heparin or low-molecular-weight heparin) initiated 24–48 hours after surgery and continued until hospital discharge, with no extended outpatient anticoagulation. Given that a substantial proportion of VTE events occur after discharge — when inpatient prophylaxis has ceased — this represents a critical and unaddressed gap in clinical care. The absence

of evidence-based guidance for this population reflects a lack of prospective data rather than a lack of biological rationale and represents an urgent research priority.

3.2 Rationale for Current Study

This study addresses the critical evidence gap regarding extended VTE prophylaxis after spinal surgery for metastatic disease. The rationale for this study is based on several key considerations:

1. *High baseline VTE risk*: The 11-15% VTE rate in this population is among the highest of any surgical cohort and exceeds thresholds where extended prophylaxis has been shown beneficial in other cancer surgery populations.
2. *Proven efficacy in analogous populations*: Extended prophylaxis with direct oral anticoagulants (DOACs) has demonstrated efficacy in reducing VTE after orthopedic surgery [9-11] and in cancer patients at high VTE risk [12-13].
3. *Favorable safety profile of apixaban*: Apixaban 2.5 mg twice daily has demonstrated a favorable bleeding profile in multiple large randomized trials, with major bleeding rates of 0.2-0.8% [9-11, 14].
4. *Convenience of oral administration*: Unlike low molecular weight heparin, which requires daily subcutaneous injections, apixaban is administered orally, improving patient acceptability and adherence.
5. *Established use in post-surgical prophylaxis*: Apixaban 2.5 mg BID is FDA-approved for VTE prophylaxis following hip and knee replacement surgery for 35 days and 12 days, respectively, establishing precedent for extended post-surgical prophylaxis with this agent.
6. *Urgent clinical need*: With approximately 15,000-20,000 spinal surgeries for metastatic disease performed annually in the United States, an evidence-based approach to VTE prophylaxis could meaningfully reduce VTE-related morbidity and mortality in this population.

This pilot study will provide the first prospective data on the safety and preliminary efficacy of extended oral anticoagulation following surgery for spinal metastases. If the study demonstrates acceptable safety and suggests benefit, it will provide the foundation for a larger, multicenter, randomized controlled trial.

3.3 Study Drug: Apixaban

3.3.1 Mechanism of Action

Apixaban is a direct, selective, reversible inhibitor of factor Xa (FXa). It inhibits both free and clot-bound FXa, thereby interrupting the coagulation cascade and reducing thrombin generation and clot formation. Apixaban does not require antithrombin III for antithrombotic activity.

3.3.2 FDA-Approved Indications

Apixaban (Eliquis) is FDA-approved for:

- Reduction of risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Prophylaxis of DVT following hip or knee replacement surgery
- Treatment of DVT and PE

- Reduction of risk of recurrent DVT and PE following initial therapy

3.3.3 Dosing for VTE Prophylaxis

The FDA-approved dose for VTE prophylaxis following hip replacement surgery is 2.5 mg orally twice daily for 35 days. For knee replacement surgery, the dose is 2.5 mg orally twice daily for 12 days. This study will approximate the hip replacement prophylaxis dose and duration (2.5 mg BID for 30 days).

3.3.4 Pharmacokinetics

- Bioavailability: ~50% for doses up to 10 mg
- Time to peak concentration: 3-4 hours
- Half-life: ~12 hours
- Protein binding: ~87%
- Metabolism: CYP3A4/5 (major), CYP1A2, 2C8, 2C9, 2C19, 2J2 (minor)
- Excretion: ~27% renal, ~56% biliary/fecal
- Substrate of P-glycoprotein (P-gp) and BCRP efflux transporters

3.3.5 Clinical Trial Experience

Apixaban has been extensively studied in the ADVANCE program (ADVANCE-1, -2, -3) for VTE prophylaxis after orthopedic surgery, enrolling over 11,000 patients. In ADVANCE-3 (hip replacement), apixaban 2.5 mg BID for 35 days demonstrated superior efficacy to enoxaparin 40 mg daily with comparable major bleeding rates (0.8% vs 0.7%) [9].

In AMPLIFY-EXT, which studied extended anticoagulation for VTE treatment, apixaban 2.5 mg BID for 12 additional months after initial VTE treatment demonstrated an 81% relative risk reduction in recurrent VTE compared to placebo, with major bleeding rates of 0.2% vs 0.5% [14].

The AVERT trial studied apixaban 2.5 mg BID for VTE prevention in ambulatory cancer patients at intermediate-to-high risk, demonstrating a 59% reduction in VTE but with increased major bleeding (3.5% vs 1.8%) compared to placebo [12]. However, this population was receiving active chemotherapy, which increases bleeding risk.

3.3.6 Safety Profile

The most common adverse reaction with apixaban is bleeding. In the ADVANCE trials using the 2.5 mg BID dose:

- Major bleeding: 0.2-0.8%
- Clinically relevant non-major bleeding: 3.0-3.5%
- Minor bleeding: 4-5%

Other adverse effects include:

- Nausea: 2-3%
- Anemia (may be related to bleeding): 1-2%
- Contusion/hematoma: 2-3%

Serious but rare adverse events include:

- Spinal/epidural hematoma (FDA black box warning for patients receiving neuraxial anesthesia or undergoing spinal puncture)
- Hypersensitivity reactions
- Hepatotoxicity (rare, generally reversible)

3.3.7 Contraindications and Drug Interactions

Apixaban is contraindicated in patients with:

- Active pathological bleeding
- Severe hypersensitivity to apixaban

Dose adjustments or avoidance is recommended with:

- Strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir)
- Strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort)

Concurrent use of antiplatelet agents, NSAIDs, or other anticoagulants increases bleeding risk.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

To determine the incidence of symptomatic venous thromboembolism (DVT or PE) within 90 days of hospital discharge in patients receiving extended prophylactic anticoagulation with apixaban 2.5 mg twice daily for 30 days after spinal surgery for metastatic disease.

4.2 Secondary Objectives

1. To determine the safety profile of apixaban 2.5 mg BID for 30 days in this population, specifically:
 - a. Incidence of major bleeding events
 - b. Incidence of clinically relevant non-major (CRNM) bleeding events
 - c. Incidence of spinal epidural hematoma
2. To assess all-cause mortality at 90 days post-discharge
3. To assess medication adherence in this population
4. To compare VTE rates in the prospective apixaban-treated cohort to historical controls who did not receive extended prophylaxis
5. To compare safety outcomes (bleeding, mortality) in the prospective cohort to historical controls

4.3 Endpoints

4.3.1 Primary Endpoint

- Incidence of symptomatic VTE (DVT and/or PE) within 90 days of hospital discharge

4.3.2 Key Secondary Endpoints

- Incidence of major bleeding events (ISTH criteria) within 90 days of discharge

- Incidence of clinically relevant non-major bleeding events (ISTH criteria) within 90 days of discharge
- All-cause mortality at 90 days post-discharge

4.3.3 Additional Secondary Endpoints

- Incidence of spinal epidural hematoma requiring intervention
- Medication adherence rate at Day 31 (based on pill count)
- VTE-related mortality
- Bleeding-related mortality
- Hospital readmission rates within 90 days
- Emergency department visits within 90 days

4.3.4 Exploratory Endpoints

- Time to VTE event
- Time to bleeding event
- Subgroup analyses by cancer type, surgical extent, hospital length of stay

5. STUDY DESIGN

5.1 Overview

This is a single-arm, prospective, open-label interventional study evaluating extended prophylactic anticoagulation with apixaban 2.5 mg twice daily for 30 days following hospital discharge in patients who have undergone spinal surgery for metastatic disease. Outcomes will be compared to a historical control cohort of similar patients who did not receive extended prophylaxis.

The study design was chosen based on several considerations:

1. The high VTE rate (11-15%) in this population provides strong biological rationale for prophylaxis
2. A placebo-controlled randomized trial would be the ideal study design but is not feasible given the small number of patients available at a single institution over a 12-month enrollment period
3. This pilot study will establish safety and provide preliminary efficacy data to inform a future randomized trial
4. A single-arm design enables more efficient enrollment and resource utilization for this initial pilot study, with results intended to inform the design and sample size of a future multicenter randomized controlled trial

5.2 Study Duration

5.2.1 Enrollment Period

Approximately 12 months to enroll 50 patients

5.2.2 Subject Participation

- Enrollment: Day of hospital discharge (after spine surgery for metastatic disease)
- Active treatment period: 30 days (apixaban 2.5 mg BID)

- Follow-up period: 61 additional days (total 91 days from discharge)
- Study completion: Day 91 post-discharge

5.2.3 Total Study Duration

Approximately 16 months (12-month enrollment + 3-month follow-up of last enrolled subject + 1-month analysis)

Expected Study Start Date: August 2026

Expected Primary Completion Date: November 2027

Expected Study Completion Date: December 2027

5.3 Historical Control Cohort

The historical control cohort consists of 68 patients who underwent spinal surgery for metastatic disease at UPMC Presbyterian and UPMC Shadyside hospitals between January 2022 and December 2024. These patients received standard perioperative care including inpatient VTE prophylaxis (typically subcutaneous heparin 5000 units TID or enoxaparin 40 mg daily) but did not receive extended prophylaxis after hospital discharge.

5.3.1 Historical Cohort Characteristics

- N = 68 patients
- Median age: [to be specified from data analysis]
- Primary cancers: [distribution to be specified]
- Surgical procedures: [distribution to be specified]
- Median hospital length of stay: [to be specified]
- 90-day VTE rate: 14.7% (10/68)
- 90-day mortality rate: 16% (11/68)

5.3.2 Historical Cohort Data Collection

Data were collected retrospectively via medical record review. VTE events were identified through:

- ICD-10 diagnosis codes for DVT (I82.4x) and PE (I26.x)
- Radiology reports documenting DVT on compression ultrasound or PE on CT pulmonary angiogram or V/Q scan
- Clinical documentation of VTE in progress notes
- Death certificates and autopsy reports where available

Bleeding events were not systematically captured in the historical cohort, limiting bleeding comparisons.

5.3.3 Historical Cohort Matching

Eligibility criteria for the prospective cohort were designed to match the characteristics of the historical cohort. The prospective cohort will be compared to the entire historical cohort; additional propensity-score matching or multivariable adjustment will be performed if significant baseline imbalances are identified.

6. SUBJECT SELECTION

6.1 Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for enrollment:

1. Age ≥ 18 years
2. Undergone spinal surgery (any approach) for treatment of vertebral metastatic disease at UPMC Presbyterian, Shadyside, or Mercy Hospital
3. Planned for discharge to home or acute rehabilitation facility (not hospice)
4. Willing and able to provide written informed consent
5. Able to take oral medications
6. Access to a telephone for follow-up calls

6.2 Exclusion Criteria

Subjects meeting ANY of the following criteria are not eligible for enrollment:

1. Already receiving therapeutic anticoagulation for another indication (e.g., atrial fibrillation, prior VTE, mechanical heart valve)
2. Planned initiation of therapeutic anticoagulation within the next 30 days for another indication
3. Known allergy or hypersensitivity to apixaban
4. History of pathological bleeding (e.g., intracranial hemorrhage, gastrointestinal bleeding requiring transfusion or endoscopic intervention within the past 6 months)
5. Active bleeding at time of planned enrollment
6. Platelet count $< 50,000/\text{mm}^3$ at time of enrollment
7. Hemoglobin < 8 g/dL at time of enrollment
8. Serum creatinine > 2.5 mg/dL
9. ALT or AST $> 3\times$ upper limit of normal
10. Total bilirubin $> 2\times$ upper limit of normal
11. Known severe hepatic impairment (Child-Pugh Class C)
12. Pregnancy or breastfeeding
13. Women of childbearing potential unwilling to use adequate contraception during study participation
14. History of proximal gastrointestinal resection (i.e. gastrectomy and/or proximal small bowel resection) that might alter oral drug absorption
15. Concurrent use of strong dual inhibitors of CYP3A4 and P-gp, or moderate CYP3A4 inhibitors:
 - Ketoconazole
 - Itraconazole
 - Ritonavir
 - Clarithromycin
 - Diltiazem (moderate CYP3A4 inhibitor; excluded for this pilot study)
16. Concurrent use of strong dual inducers of CYP3A4 and P-gp:
 - Rifampin
 - Carbamazepine
 - Phenytoin

- St. John's Wort
- 17. Inability to safely discontinue all antiplatelet medications for the 30-day study drug period, as determined by the treating cardiologist or prescribing physician:
 - Aspirin
 - Clopidogrel (Plavix)
 - Ticagrelor (Brilinta)
- 18. Inability or unwillingness to discontinue chronic NSAID during the 30-day study drug period (as-needed NSAID use <3 days/week is acceptable)
- 19. Planned surgery or invasive procedure within the next 30 days
- 20. Hospital length of stay ≥30 days (inpatient prophylaxis continues throughout hospitalization; these patients do not require extended prophylaxis)
- 21. Prisoner or incarcerated individual
- 22. Any other condition that, in the investigator's opinion, would make the subject unsuitable for study participation or unable to comply with study procedures

6.3 Vulnerable Populations

This study will enroll patients with metastatic cancer, who may be considered vulnerable due to serious illness and limited life expectancy. Special protections include:

- Emphasis during consent process that participation is voluntary and will not affect clinical care
- Opportunity to involve family members/caregivers in the consent discussion
- Verification of decision-making capacity prior to consent
- Right to withdraw at any time without penalty
- Ongoing assessment of continued appropriateness of participation

Pregnant women, children, and prisoners are excluded.

7. TREATMENT PLAN

7.1 Study Drug Administration

7.1.1 Study Drug

Apixaban (Eliquis) 2.5 mg oral tablets

7.1.2 Dose and Schedule

2.5 mg orally twice daily (morning and evening) for 30 days

7.1.3 Treatment Initiation

Apixaban will be prescribed on the day of hospital discharge (Day 0). The first dose should be taken on Day 1 (the day after discharge). If the patient is discharged in the evening, the first dose may be taken the evening of discharge if more than 12 hours have elapsed since the last dose of inpatient pharmacologic prophylaxis (e.g., enoxaparin, heparin).

7.1.4 Treatment Duration

30 days from first dose

7.1.5 Drug Supply

Apixaban will be supplied by the study and provided to subjects at no cost. The study drug will be stored and dispensed by the UPMC Shadyside Investigational Drug Service (IDS) under patient-specific labeling. On the day of discharge, a member of the study team will obtain the dispensed study drug from IDS and deliver it to the subject.

Subjects will not be charged for the study medication and insurance will not be billed for it; drug costs are covered by the study sponsor (Beckwith Institute Frontline Innovation Program).

7.1.6 Dose Modifications

No dose modifications are planned in this study. The 2.5 mg BID dose was specifically chosen to match the FDA-approved prophylactic dose and should not require adjustment even in patients with borderline renal function or low body weight, based on FDA labeling.

7.1.7 Treatment Discontinuation Criteria

Apixaban should be discontinued if any of the following occur:

- Major bleeding event
- Spinal epidural hematoma
- Need for urgent surgery or invasive procedure
- Platelet count drops to $<50,000/\text{mm}^3$
- Development of severe renal impairment
- Initiation of a prohibited concomitant medication (i.e. strong CYP3A4/P-gp inhibitor or inducer, antiplatelets, or anticoagulants)
- Subject withdrawal of consent
- Investigator determination that continued treatment is not in subject's best interest

If apixaban is discontinued for any reason, the subject will continue in follow-up for safety assessments unless consent is withdrawn.

7.2 Concomitant Medications

7.2.1 Medications Requiring Caution

The following medications increase bleeding risk when used with apixaban; concurrent use will be documented and subjects will be counseled on bleeding precautions:

- NSAIDs (chronic use is excluded; as-needed use <3 days/week is permitted)
- SSRIs and SNRIs
- Systemic cancer chemotherapy (particularly agents affecting platelet production)

7.2.2 Dose Adjustments for Drug Interactions

Per FDA labeling, apixaban should be dose-reduced if patients have 2 of 3 characteristics: age ≥ 80 , body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL. However, this applies only to the atrial fibrillation indication (5 mg BID dose). The 2.5 mg BID prophylactic dose used in this study does not require further reduction.

7.3 Prohibited Medications

The following medications are PROHIBITED during study participation:

- Other anticoagulants (warfarin, other DOACs, heparin, LMWH) except for treatment of VTE that develops during study
- Antiplatelet medications: aspirin, clopidogrel (Plavix), ticagrelor (Brilinta)
- Strong dual CYP3A4 and P-gp inhibitors, and moderate CYP3A4 inhibitors: ketoconazole, itraconazole, ritonavir, clarithromycin, diltiazem (excluded for this pilot study)
- Strong dual CYP3A4 and P-gp inducers: rifampin, carbamazepine, phenytoin, St. John's Wort

If a prohibited medication must be initiated for clinical reasons, the study drug should be discontinued and the subject will continue in follow-up.

7.4 Drug Accountability

Drug accountability will be maintained via:

1. IDS dispensing record documenting the study drug dispensed for each subject
2. Study team delivery log documenting transfer of the study drug from IDS to the subject at discharge (date of delivery, study team member, confirmation of subject receipt)
3. Day 2 phone call: confirm the subject has started taking the medication
4. Day 31 phone call: self-reported pill count (patient reports how many pills remain, expected count should be 0)

Adherence will be calculated as: $(60 - \text{remaining pills}) / 60 \times 100\%$

Adherence $\geq 80\%$ (≤ 12 pills remaining) will be considered acceptable.

Unused study drug will be disposed of by the subject; if required by IDS, subjects will instead be instructed to return unused study drug to IDS for accountability and destruction.

8. STUDY PROCEDURES AND ASSESSMENTS

8.1 Screening and Enrollment

8.1.1 Pre-Screening (Waiver of Consent)

The research team will review operating room schedules at UPMC Presbyterian, Shadyside, and Mercy to identify patients undergoing spinal surgery for metastatic disease. Medical records will be reviewed under a waiver of consent to assess preliminary eligibility based on:

- Diagnosis of spinal metastatic disease
- Type of surgical procedure
- Major exclusion criteria (pregnancy, active therapeutic anticoagulation, severe renal/hepatic impairment)

Patients who appear potentially eligible will be flagged and approached at the appropriate time (typically a day or two following surgery or rarely the day of surgery in the case of an outpatient surgery).

8.1.2 Approach and Consent

Eligible patients will be approached by the PI or a trained co-investigator (senior neurosurgery resident) to discuss study participation. This will occur during the hospitalization, ideally at least 24-48 hours before anticipated discharge to allow time for consideration.

The informed consent discussion will include:

- Purpose of the study
- Study procedures and time commitment
- Risks and benefits of participation
- Voluntary nature of participation
- Insurance coverage and costs
- Alternative options
- Right to withdraw

Patients will be provided with a copy of the consent form to review and discuss with family/caregivers.

8.1.3 Enrollment Visit (Day 0 - Day of Discharge)

On the day of planned discharge, the study team will:

1. Verify continued eligibility (review interval history, labs, new medications)
2. Assess decision-making capacity:
 - Patient is alert and oriented
 - Patient can explain key points of the study (teach-back)
 - No signs of delirium or severe cognitive impairment
 - Not within 12 hours of general anesthesia or procedural sedation
3. Obtain written informed consent
4. Collect baseline data (see Section 8.2)
5. Provide study drug (apixaban 2.5 mg BID for 30 days), dispensed by IDS and delivered to the subject by the study team at no cost
 - Study drug obtained from IDS and delivered to the subject; delivery documented
 - Instructions provided: take 1 tablet by mouth twice daily (morning and evening) for 30 days starting tomorrow
6. Provide patient education:
 - Bleeding precautions and warning signs
 - 24-hour emergency contact information
 - Study team contact information
 - Schedule of follow-up phone calls
7. Verify patient contact information (phone numbers, alternate contact)

8.2 Baseline Assessments (Day 0)

The following data will be collected at enrollment:

8.2.1 Demographics

- Age, sex, race, ethnicity
- Weight, height, BMI

- Contact information (address, phone numbers, alternate contact)

8.2.2 Medical History

- Primary cancer diagnosis
- Date of initial cancer diagnosis
- Prior cancer treatments (surgery, chemotherapy, radiation)
- Metastatic disease sites
- ECOG performance status
- Comorbidities: hypertension, diabetes, coronary artery disease, prior VTE, prior stroke/TIA, atrial fibrillation
- Current medications (complete list)
- Smoking status

8.2.3 Surgical Details

- Date of surgery
- Spinal level(s) operated
- Surgical approach (anterior, posterior, lateral)
- Type of procedure (decompression, fusion, instrumentation, vertebrectomy, etc.)
- Estimated blood loss
- Operative time
- Intraoperative complications

8.2.4 Hospitalization Details

- Date of surgery
- Date of discharge
- Hospital length of stay
- Postoperative complications
- Type and duration of inpatient VTE prophylaxis (e.g., heparin 5000 units SC TID from POD 1 to discharge)
- Need for blood product transfusion (units transfused, dates of transfusion)
- ICU stay (yes/no, duration)
- Discharge disposition (home, acute rehab)
- Mobility at discharge (ambulatory, walker, wheelchair, bedbound)

8.2.5 Laboratory Values (Most recent prior to discharge)

- Hemoglobin
- Platelet count
- Serum creatinine, eGFR
- ALT, AST
- Total bilirubin
- INR (if available)

8.3 Follow-up Assessments

8.3.1 Day 2 Post-Discharge (call window: Day 2 to Day 4)

Telephone call by research coordinator or study team member

Duration: Approximately 5-10 minutes

Assessment:

- Confirm subject received study drug at discharge (per delivery log) - Did patient start taking apixaban? (yes/no)
 - If no: reason
 - If yes: date of first dose
- Any symptoms of VTE?
 - Leg swelling, pain, warmth, redness (DVT symptoms)
 - Chest pain, shortness of breath (PE symptoms)
- Any bleeding events since discharge?
- Major bleeding (as defined in Section 9.2.1)
 - specific questions
- CRNM bleeding (as defined in Section 9.2.2)
 - specific questions
- Minor bleeding
 - Any bleeding requiring medical attention?
 - Any bleeding requiring study drug discontinuation?
- Any new neurological symptoms? (back pain, leg weakness, numbness, bowel/bladder dysfunction - concerning for epidural hematoma)
- Any other adverse events or health problems?
- Any new medications started?
- Any emergency department visits or hospitalizations since discharge?

Action items:

- If bleeding symptoms present: assess severity, advise to contact surgeon or seek emergency care if severe
- If VTE or epidural hematoma symptoms: advise immediate emergency department evaluation
- Document all findings in REDCap

8.3.2 Day 31–33 Post-Discharge (call window: Day 31 to Day 33)

Telephone call by research coordinator or study team member

Duration: Approximately 5-10 minutes

Assessment:

- Medication adherence:
- Did patient complete the 30-day course? (yes/no)
 - If no: date stopped, reason stopped
- Pill count: “How many pills do you have left?” (should be 0)
- Any bleeding events since Day 31?
 - Major, CRNM, or minor bleeding
- Any VTE events?
 - DVT diagnosed (date, location, diagnostic test)
 - PE diagnosed (date, diagnostic test)
- Any new neurological symptoms concerning for epidural hematoma? - Any other adverse events?
- Any new medications started?
- Any emergency department visits since Day 2? (dates, reasons)

- Any hospitalizations since Day 2? (dates, reasons, diagnoses)
- Any deaths in patient's immediate contacts (in case patient has died and family answers phone)

Action items:

- If VTE event occurred: obtain medical records authorization to review imaging and treatment
- If bleeding event occurred: obtain details, assess whether it meets major or CRNM criteria, obtain medical records if treated at outside facility
- If patient stopped medication early: document reason, assess whether adverse event reporting needed - Document all findings in REDCap

8.3.3 Day 91 Post-Discharge (call window: Day 91 to Day 97)

Telephone call by research coordinator or study team member Duration: Approximately 5-10 minutes

Assessment:

- Any bleeding events since Day 31?
 - Major, CRNM, or minor bleeding
- Any VTE events since Day 31?
 - DVT diagnosed (date, location, diagnostic test)
 - PE diagnosed (date, diagnostic test)
- Any new neurological symptoms concerning for epidural hematoma? - Any other adverse events?
- Any new medications started?
- Any emergency department visits since Day 31? (dates, reasons)
- Any hospitalizations since Day 31? (dates, reasons, diagnoses)
- Vital status: alive vs deceased
 - If deceased: date of death, cause of death (if known)

Action items:

- If VTE or bleeding event occurred: obtain medical records
- If patient deceased: obtain death certificate if available, review medical records for cause of death
- Document all findings in REDCap
- Study participation complete

8.3.4 Medical Record Review (Throughout study period and at Day 91) The research team will periodically review UPMC medical records for all enrolled patients to identify:

- VTE events (review imaging reports, ICD-10 codes)
- Bleeding events (review ED visits, admissions, imaging)
- Deaths (review medical records, death certificates)
- Any other significant clinical events

For any significant events (VTE, major bleeding, CRNM bleeding, death), detailed information will be abstracted from the medical record.

For care received at non-UPMC facilities, written authorization will be obtained from the patient to request outside medical records.

8.4 Schedule of Events

Procedure/Assessment	Screening	Baseline (Day 0)	Day 2-4	Day 31-33	Day 91-97	Unscheduled
Eligibility assessment	X	X				
Informed consent		X				
Demographics		X				
Medical history	X	X				
Surgical details	X	X				
Labs (CBC, Chem)	X	X				If clinically indicated
Study drug dispensed/delivered		X				
Patient education		X				
Medication initiation check			X			
Pill count/adherence				X		
VTE assessment			X	X	X	If symptoms
Bleeding assessment			X	X	X	If symptoms
Neurological assessment			X	X	X	If symptoms
Adverse event assessment			X	X	X	X
Healthcare utilization			X	X	X	
Vital status				X	X	
Medical record review	X	X	X	X	X	As needed

8.5 Subject Completion and Withdrawal

8.5.1 Study Completion

A subject is considered to have completed the study if they:

- Complete the 30-day apixaban course (or document reason for early discontinuation)
- Complete all three follow-up phone calls (Days 2, 31, 91)
- Provide outcome data through Day 91

8.5.2 Early Withdrawal

Subjects may withdraw from the study at any time for any reason. Reasons for withdrawal include:

- Subject decision (voluntary withdrawal)
- Lost to follow-up (unable to contact after 3 attempts at each timepoint)
- Death
- Investigator decision (continued participation not in subject's best interest)

When a subject withdraws:

- Date and reason for withdrawal will be documented
- Subject will be asked permission for continued medical record review for safety outcomes

- Data collected prior to withdrawal will be retained and analyzed unless subject specifies that it should be deleted/destroyed

8.5.3 Lost to Follow-Up

If a subject cannot be reached by phone, the research team will:

1. Attempt contact at all provided phone numbers (up to 3 attempts per number)
2. Contact alternate contact person if provided
3. Leave voicemail (if permitted by subject) requesting callback
4. Check UPMC medical records for any clinical encounters
5. Check publicly available records (obituaries) if unable to contact

After 3 contact attempts over a 1-week period, the subject will be considered lost to follow-up for that timepoint. Medical record review will continue.

9. OUTCOME DEFINITIONS

All outcomes will be adjudicated by the Principal Investigator based on objective diagnostic testing, medical record documentation, and clinical reports. Definitions are adapted from the International Society on Thrombosis and Haemostasis (ISTH) criteria and have been used in major anticoagulant clinical trials.

9.1 Venous Thromboembolism

9.1.1 Deep Vein Thrombosis (DVT)

A DVT is defined as a new symptomatic venous thrombus in the lower or upper extremity confirmed by ONE of the following:

For a NEW DVT:

1. Abnormal compression ultrasound (CUS) demonstrating non-compressibility of a vein, OR
2. Intraluminal filling defect on venography

For a RECURRENT DVT (in a previously affected limb):

1. Abnormal CUS where compression had been normal at baseline, OR
2. If non-compressible during screening, a substantial increase (≥ 4 mm) in diameter of the thrombus during full compression, OR
3. Extension of an intraluminal filling defect on venography, OR
4. New intraluminal filling defect on venography, OR
5. Extension of non-visualization of veins in the presence of a sudden cutoff on venography

DVTs will be classified as:

- Proximal (popliteal, femoral, iliac veins)
- Distal (calf veins only)
- Upper extremity

9.1.2 Pulmonary Embolism (PE)

A PE is defined as symptoms of PE with ONE of the following findings:

1. A new intraluminal filling defect in segmental or more proximal branches on spiral computed tomography (CT) of the chest, OR
2. A new intraluminal filling defect or extension of an existing defect, or a new sudden cutoff of vessels >2.5 mm in diameter on pulmonary angiography, OR
3. A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation-perfusion lung scintigraphy (V/Q scan), OR
4. Inconclusive spiral CT, pulmonary angiography, or V/Q scan evidence of PE with demonstration of a new DVT in the lower extremities by CUS or venography

PE will be classified as:

1. Massive (causing hemodynamic instability requiring vasopressors or resulting in cardiac arrest)
2. Submassive (with right ventricular dysfunction on imaging or elevated troponin)
3. Low-risk (neither massive nor submassive)

9.1.3 VTE Not Requiring Imaging Confirmation

In the following circumstances, VTE may be adjudicated without confirmatory imaging:

1. PE diagnosed at autopsy
2. Sudden unexplained death where PE cannot be ruled out
3. Death within 30 days of symptoms consistent with PE where PE is listed as primary or contributing cause of death on death certificate

9.2 Bleeding Events

All bleeding events will be classified according to ISTH criteria as major, clinically relevant non-major (CRNM), or minor.

9.2.1 Major Bleeding

A major bleeding event is defined as acute clinically overt bleeding accompanied by ONE OR MORE of the following:

1. A decrease in hemoglobin of ≥ 2 g/dL over a 24-hour period, OR
2. A transfusion of ≥ 2 units of packed red blood cells or whole blood, OR
3. Bleeding that occurs in at least ONE of the following critical sites:
 - Intracranial (intracerebral, subdural, subarachnoid, epidural)
 - Intrapinal (epidural or subdural)
 - Intraocular (within the corpus of the eye, excluding conjunctival bleeding)
 - Pericardial
 - Intra-articular
 - Intramuscular with compartment syndrome
 - Retroperitoneal, OR
4. Bleeding that is fatal (directly causes or contributes to death)

9.2.2 Clinically Relevant Non-Major (CRNM) Bleeding

CRNM bleeding is defined as acute clinically overt bleeding that does NOT meet criteria for major bleeding but meets ONE OR MORE of the following:

1. Bleeding compromising hemodynamics (requiring IV fluids or causing symptomatic hypotension)
2. Bleeding leading to hospitalization or prolongation of existing hospitalization
3. Bleeding leading to emergency department visit
4. Subcutaneous hematoma $>25\text{ cm}^2$ (or $>100\text{ cm}^2$ if traumatic cause documented)
5. Intramuscular hematoma documented by ultrasound, CT, or MRI
6. Epistaxis lasting >5 minutes, or repetitive (≥ 2 episodes more extensive than spots on a handkerchief within 24 hours), or leading to intervention (packing or cauterization)
7. Gingival bleeding occurring spontaneously (unrelated to eating or tooth brushing) or lasting >5 minutes
8. Hematuria that is macroscopic and spontaneous, or lasting >24 hours after instrumentation of the urogenital tract
9. Macroscopic gastrointestinal hemorrhage, including at least one episode of rectal blood loss more than a few spots on toilet paper
10. Hemoptysis more than a few speckles in sputum and not occurring in context of PE
11. Any other bleeding requiring medical intervention, unscheduled physician contact, temporary or permanent cessation of study drug, or associated with pain or impairment of activities of daily living

9.2.3 Minor Bleeding

Minor bleeding is defined as any acute clinically overt bleeding that does NOT meet criteria for major bleeding or CRNM bleeding.

Examples include:

- Brief self-limited epistaxis (<5 minutes, no intervention)
- Small bruises or petechiae
- Minimal blood-tinged sputum
- Minimal hematuria lasting <24 hours after catheterization
- Small amount of blood with bowel movement not requiring evaluation
- Bleeding from minor cuts or abrasions
- Minimal gingival bleeding with tooth brushing

9.2.4 Fatal Bleeding

A fatal bleeding event is a bleeding event that is determined to be the primary cause of death or contributed directly to death.

9.2.5 Adjudication of Bleeding Events

All reported bleeding events will be adjudicated by the Principal Investigator based on:

- Medical records
- Laboratory data (hemoglobin, transfusion records)
- Imaging reports
- Emergency department/hospitalization records
- Telephone interview documentation

In cases of uncertainty, events will be classified conservatively (e.g., if unclear whether CRNM vs minor, classify as CRNM).

9.3 Death

9.3.1 All-Cause Mortality

Death from any cause within 90 days of hospital discharge.

9.3.2 Cause-Specific Mortality

For all deaths, the cause will be adjudicated to one of the following categories based on medical records, death certificates, and autopsy reports (when available):

1. VTE-related death
 - PE confirmed by imaging, autopsy, or high clinical suspicion
 - Unexplained sudden death where VTE cannot be ruled out
2. Bleeding-related death
 - Death directly caused by major bleeding event
 - Death to which bleeding contributed (e.g., hemorrhagic stroke, fatal GI bleed)
3. Cancer-related death
 - Progressive metastatic disease
 - Complications of cancer (e.g., bowel obstruction, pathologic fracture)
4. Treatment-related death (non-bleeding)
 - Complications of surgery
 - Chemotherapy or radiation complications
5. Cardiovascular death (non-PE)
 - Myocardial infarction
 - Ischemic stroke
 - Heart failure
 - Arrhythmia
6. Infection-related death
 - Sepsis
 - Pneumonia
7. Other known cause
 - To be specified
8. Unknown cause
 - Insufficient information to determine cause

10. ADVERSE EVENT REPORTING

10.1 Definitions

10.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject administered a study intervention, which does not necessarily have a causal relationship with the treatment.

An AE can be:

- Any unfavorable and unintended sign (including abnormal laboratory finding)

- Symptom
- Disease temporally associated with the use of the study drug

10.1.2 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that:

- Results in death
- Is life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is an important medical event that may jeopardize the subject or require intervention to prevent one of the above outcomes

For this study, the following events are considered SAEs:

- Death (any cause)
- Major bleeding (as defined in Section 9.2.1)
- VTE (DVT or PE)
- Spinal epidural hematoma requiring intervention
- Any hospitalization (except elective procedures planned before enrollment)
- Any emergency department visit resulting in hospital admission

10.1.3 Unexpected Adverse Event

An adverse event is considered unexpected if it is not listed in the current investigator brochure or, for an approved drug like apixaban, is not consistent with the FDA-approved labeling.

10.1.4 Related Adverse Event

An adverse event is considered related to the study intervention if there is a reasonable possibility that the event was caused by the study drug. Relationship categories:

- Definite: Clear causal relationship
- Probable: Likely causal relationship
- Possible: Causal relationship cannot be ruled out
- Unlikely: Doubtful causal relationship
- Not related: Clearly not caused by study drug

10.2 Adverse Event Assessment

10.2.1 AE Collection Period

Adverse events will be collected from the time of first dose of apixaban (Day 1) through Day 91 post-discharge (end of study participation).

10.2.2 Severity Grading

Adverse events will be graded using CTCAE v5.0 (Common Terminology Criteria for Adverse Events):

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening

- Grade 5: Death

For bleeding events, ISTH classification (major, CRNM, minor) will be used as the primary severity grading.

10.2.3 Assessment at Each Contact

At each follow-up phone call and throughout the study period, subjects will be asked about:

- Any new symptoms or health problems
- Any bleeding events
- Any symptoms of blood clots
- Any emergency department visits
- Any hospitalizations
- Any new medications
- Any other health changes

All reported AEs will be documented in the study database with:

- Event description
- Date of onset
- Date of resolution (or ongoing)
- Severity grade
- Relationship to study drug
- Action taken (none, drug held, drug discontinued, treatment given)
- Outcome (resolved, ongoing, sequelae, death)

10.3 Serious Adverse Event Reporting

10.3.1 SAE Reporting to IRB

All SAEs will be reported to the University of Pittsburgh IRB according to HRPO policies:

- Unanticipated problems involving risks to subjects or others: Within 7 days of PI becoming aware
- Expected SAEs: In accordance with IRB-approved schedule (at continuing review)
- Deaths: Within 7 days

10.3.2 SAE Reporting to Sponsor

All SAEs will be reported to the study sponsor (Beckwith Institute) within 7 days of PI becoming aware.

10.3.3 SAE Reporting to FDA

This study is being conducted under an IND exemption per 21 CFR 312.2(b). As an IND-exempt study, expedited safety reporting to FDA under 21 CFR 312.32 is not required. All serious adverse events will be reported to the University of Pittsburgh IRB per HRPO policies and to the study sponsor (Beckwith Institute) within 7 days of the PI becoming aware.

10.3.4 SAE Documentation For each SAE, the following will be documented:

- SAE report form (completed by PI)
- Supporting medical records (discharge summaries, imaging reports, lab results)
- Assessment of relationship to study drug
- Assessment of expectedness
- Action taken
- Outcome

10.4 Special Reporting Situations

10.4.1 Spinal Epidural Hematoma

Any spinal epidural hematoma, regardless of whether it requires intervention, will be reported as an SAE within 48 hours. The PI will immediately review the case to determine whether study enrollment should be suspended pending safety review.

10.4.2 Pregnancy

Women of childbearing potential are required to use contraception during study participation. If a pregnancy is discovered during the study:

- Apixaban will be discontinued immediately (FDA pregnancy category B; use during pregnancy not recommended)
- The pregnancy will be followed to outcome
- Pregnancy outcome will be reported to the sponsor and IRB

10.4.3 Death

All deaths will be reported to the IRB and sponsor within 7 days. Cause of death will be determined by review of medical records, death certificates, and autopsy reports (if available). Relationship to study drug will be assessed by the PI.

11. DATA AND SAFETY MONITORING

11.1 Safety Monitoring Plan

Given the greater-than-minimal-risk nature of this study and the vulnerable population (patients with metastatic cancer), a formal data and safety monitoring plan is required.

11.1.1 Safety Monitoring Structure

The Principal Investigator will serve as the primary safety monitor with oversight from a designated independent safety monitor.

Independent Safety Monitor:

Dr. Kalil Abdullah – UPMC Department of Neurosurgery and Hillman Cancer center
A neurosurgeon that is not involved in the study who has expertise in neurosurgical oncology and clinical trial safety.

11.1.2 Ongoing Safety Monitoring

The PI will review all adverse events on an ongoing basis (weekly during active enrollment). The following will be monitored:

- All SAEs (especially major bleeding and spinal epidural hematoma)
- Trends in CRNM bleeding events

- Unanticipated problems
- Protocol deviations
- Subject withdrawals due to adverse events

11.1.3 Safety Review Meetings

Formal safety reviews will be conducted:

- After enrollment of the first 10 patients complete 91-day follow-up
- After enrollment of 25 patients complete 91-day follow-up
- After completion of enrollment (50 patients enrolled)
- Ad hoc if triggered by stopping rules (see Section 11.2)

Each safety review will include:

- Tabulation of all SAEs
- Analysis of bleeding events (major, CRNM, minor)
- Analysis of VTE events
- Deaths and causes of death
- Assessment of risk-benefit balance
- Recommendation: continue, modify protocol, or stop study

The independent safety monitor will review the data and provide a recommendation to the PI with submission of a written recommendation to the IRB if any concerns arise.

11.2 Stopping Rules

The study will be stopped or suspended if any of the following occurs:

11.2.1 Unacceptable Bleeding Rate

Based on ADVANCE trial data, major bleeding is expected in <1% of patients (likely 0-1 events in 50 patients). CRNM bleeding is expected in approximately 3% of patients (1-2 events in 50 patients).

STOPPING RULE:

- If ≥ 2 major bleeding events occur, enrollment will be paused for safety review
- If ≥ 4 CRNM bleeding events occur, enrollment will be paused for safety review

11.2.2 Catastrophic Bleeding Event

- Any single fatal bleeding event will trigger immediate safety review

11.2.3 Higher Than Expected VTE Rate

If the VTE rate in the apixaban-treated cohort exceeds the historical control rate (>14.7%), this suggests lack of efficacy and the study will be reviewed for potential futility.

11.2.4 External Safety Concerns

If new safety information about apixaban emerges from other studies or post-marketing surveillance that impacts the risk-benefit assessment for this study, enrollment may be suspended pending review.

11.3 Data Monitoring

11.3.1 Data Quality

The research coordinator will perform ongoing data quality checks:

- Completeness: Ensure all CRFs are completed for each subject
- Consistency: Check for internal inconsistencies
- Accuracy: Verify key data points against source documents
- Timeliness: Ensure data entry occurs within 7 days of data collection

The PI will review data quality monthly.

11.3.2 Protocol Deviations

Any deviation from the protocol will be documented and categorized as:

- Minor deviation: Does not affect subject safety or data integrity (e.g., phone call outside of visit window)
- Major deviation: Could affect subject safety or data integrity (e.g., enrolling ineligible subject, missing major assessment)

Major deviations will be reported to the IRB per HRPO policies.

11.3.3 Audit and Monitoring

The study may be subject to audit by:

- University of Pittsburgh Office of Research Protections
- UPMC Quality Assurance
- Study sponsor (Beckwith Institute)
- FDA (if IND is required)

All study records will be available for audit.

12. STATISTICAL CONSIDERATIONS

12.1 Sample Size Justification

12.1.1 Rationale for Sample Size This is a pilot/feasibility study designed to provide preliminary evidence of safety and efficacy to inform a future randomized controlled trial. Sample size was determined based on:

1. Expected VTE rate in historical controls: 14.7% (10/68)
2. Expected VTE rate with apixaban treatment: ~5% (based on ADVANCE trials showing ~70% VTE reduction)
3. Feasibility of enrollment over 12 months at UPMC: ~50 subjects

12.1.2 Bayesian Analysis for Sample Size

A Bayesian analysis was performed to calculate the likelihood that extended prophylactic anticoagulation is superior based on the expected risk ratio compared to historical data.

The incidence of symptomatic VTE within 30 days is known for the historical cohort, consisting of 10 cases among 68 treated patients (14.7%). The tables below show estimated probabilities of inferring superiority at different sample sizes of 50 or 40 patients treated with the extended prophylactic anticoagulation regimen. As seen, with 50 patients treated with extended prophylactic anticoagulation, an observed 46% reduction in the incidence of symptomatic VTE within 30 days of surgery would provide an 85.2% probability of being better than the historical approach, and an observed 59% reduction in the incidence of symptomatic VTE within 30 days of surgery would provide a 92.3% probability of being better than the historical approach. With 40 patients treated with extended prophylactic anticoagulation, an observed 49% reduction in the incidence of symptomatic VTE within 30 days of surgery would provide an 84.6% probability of being better than the historical approach, and an observed 66% reduction in the incidence would provide a 92.8% probability of being better than the historical approach.

p (Standard Group)	p (Extended Group)	Standard Group N/cases	Extended Group N/cases	Risk Ratio (Extended vs. Standard)	% Reduction with Extended Regimen	Probability p that (Extended Prophylactic is Better)
0.147	0.060	68/10	50/3	0.41	-59%	92.3%
0.147	0.080	68/10	50/4	0.54	-46%	85.2%
0.147	0.100	68/10	50/5	0.68	-32%	76.1%
0.147	0.120	68/10	50/6	0.82	-18%	64.3%
Signal of Potential Harm in the Extended Group						
Major Bleed: 2 or more of the 50 treated cases.						
Clinically relevant, Non-Major Bleeding: 4 or more of the 50 treated cases.						

p (Standard Group)	p (Extended Group)	Standard Group N/cases	Extended Group N/cases	Risk Ratio (Extended vs. Standard)	% Reduction with Extended Regimen	Probability p that (Extended Prophylactic is Better)
0.147	0.050	68/10	40/2	0.34	-66%	92.8%
0.147	0.075	68/10	40/3	0.51	-49%	84.6%
0.147	0.100	68/10	40/4	0.68	-32%	73.1%
0.147	0.125	68/10	40/5	0.85	-15%	59.7%
Signal of Potential Harm in the Extended Group						
Major Bleed: 2 or more of the 40 treated cases.						
Clinically relevant, Non-Major Bleeding: 3 or more of the 40 treated cases.						

The ADVANCE trial showed a 70% reduction in VTE, which would yield a greater than 92.8% probability of being better with a sample size of 40. Given that we would expect to enroll 50 subjects during one year and the mortality-adjusted sample size described below, a total sample size of 50 subjects seemed a reasonable number to balance likelihood of a positive result and the expected duration needed for enrollment. For instance, even with a smaller reduction than seen in ADVANCE, for instance 50%, a sample size of 40 would still yield a 85% probability of benefit.

12.1.3 Mortality-Adjusted Sample Size

The historical cohort had 16% (11/68) mortality at 90 days. To account for potential attrition from death or loss to follow-up, the target enrollment is 50 patients, which should yield approximately 40-42 patients with complete 90-day follow-up.

12.1.4 Power Considerations

This pilot study is not powered for a formal hypothesis test. However, for reference:

- To detect a reduction in VTE from 14.7% to 5% with 80% power and $\alpha=0.05$ (two-sided) would require approximately 200 patients per group
- This pilot study will provide effect size estimates and confidence intervals to inform sample size calculations for a future definitive RCT

12.2 Analysis Populations

12.2.1 Safety Population All subjects who receive at least one dose of apixaban. This is the primary population for safety analyses.

12.2.2 Intention-to-Treat (ITT) Population All subjects who are enrolled and provided apixaban, regardless of whether they actually take the medication. This is the primary population for efficacy analyses.

12.2.3 Per-Protocol Population

All subjects who:

- Complete at least 25 days of apixaban treatment ($\geq 83\%$ of course)
- Have complete 90-day follow-up data
- Have no major protocol deviations affecting primary outcome ascertainment

12.2.4 Historical Control Population

All 68 patients in the historical cohort who meet the same eligibility criteria as the prospective cohort. Additional patients that met the eligibility criteria between this analysis and the start of enrollment will be added to the historical control population.

12.3 Statistical Analysis Plan

12.3.1 Descriptive Statistics Continuous variables will be summarized with:

- Mean $\pm$ standard deviation (for normally distributed variables)
- Median [interquartile range] (for non-normally distributed variables)

Categorical variables will be summarized with:

- Frequency (n) and percentage (%)

12.3.2 Baseline Characteristics

Baseline characteristics will be compared between the prospective apixaban cohort and historical control cohort using:

- Student's t-test or Wilcoxon rank-sum test for continuous variables
- Chi-square test or Fisher's exact test for categorical variables

If significant imbalances are identified, propensity score matching or multivariable adjustment will be performed.

12.3.3 Primary Endpoint Analysis

The primary endpoint is the incidence of VTE within 90 days of hospital discharge.

Primary analysis:

- Calculate VTE rate in prospective cohort: $n/N \times 100\%$
- Compare to historical control rate: $10/68 = 14.7\%$
- Calculate risk difference and 95% confidence interval
- Calculate risk ratio and 95% confidence interval
- Bayesian analysis: Calculate posterior probability that apixaban reduces VTE risk

We assume that patients previously treated in the historical cohort will be similar to those treated with the extended prophylactic anticoagulation. To the extent possible, chart reviews will be conducted to confirm this assumption. For the primary analysis, a Bayesian comparison of the two binomial proportions (historical group and new cohort) of the incidence of symptomatic VTE within 30 days of surgery will be conducted.

Although we postulate a better outcome with the extended prophylactic anticoagulation regimen, we will conservatively use a uniform prior distribution which assumes no prior knowledge of the effectiveness of the extended prophylactic anticoagulation regimen (i.e., the distributions are shaped purely by the observed data).

Bayesian analysis:

- Use uniform (non-informative) prior distribution
- Calculate posterior distribution of risk ratio
- Report posterior probability that $RR < 1.0$ (any benefit)
- Report posterior probability that $RR < 0.7$ (clinically meaningful benefit)

12.3.4 Secondary Endpoint Analyses

Bleeding Events:

- Major bleeding rate (with 95% CI)
- CRNM bleeding rate (with 95% CI)
- Combined major + CRNM bleeding rate
- Comparison to historical controls (if data available)
- Comparison to ADVANCE trial benchmarks

All-Cause Mortality:

- 90-day mortality rate (with 95% CI)
- Comparison to historical control rate: 16% (11/68)
- Cause-specific mortality rates

Medication Adherence:

- Proportion with $\geq 80\%$ adherence (≤ 12 pills remaining at Day 31)
- Mean % adherence

12.3.5 Time-to-Event Analyses

Time to VTE and time to major bleeding will be analyzed using Kaplan-Meier methods. Survival curves will be generated for the prospective cohort. Log-rank test will compare the prospective cohort to historical controls (if time-to-event data available in historical cohort).

12.3.6 Subgroup Analyses (Exploratory)

The following subgroup analyses are planned (exploratory, hypothesis-generating):

- VTE rate by primary cancer type (lung, breast, prostate, renal, other)
- VTE rate by surgical extent (decompression only vs fusion/instrumentation)
- VTE rate by mobility at discharge (ambulatory vs non-ambulatory)
- VTE rate by hospital length of stay (<7 days vs ≥7 days)

These analyses will be descriptive due to small sample sizes.

12.3.7 Propensity Score Analysis

If significant baseline imbalances exist between the prospective and historical cohorts, propensity score matching or inverse probability weighting will be performed. Variables for propensity score model:

- Age
- Sex
- Primary cancer type
- Number of spinal levels operated
- Surgical approach
- Hospital length of stay
- Mobility at discharge
- Comorbidities

12.3.8 Handling of Missing Data

Primary analysis will use available data (complete case analysis). Sensitivity analyses will be performed:

- Best case: Assume all missing VTE outcomes are negative (no VTE)
- Worst case: Assume all missing VTE outcomes are positive (VTE occurred)

For subjects lost to follow-up, medical record review will attempt to ascertain outcomes.

12.3.9 Interim Analyses

Safety reviews will occur after 10 and 25 patients complete follow-up. No alpha adjustment will be made for multiple looks as this is a pilot study and p-values are descriptive.

12.3.10 Final Analysis

Final analysis will occur after all 50 subjects complete 91-day follow-up (or are censored due to death or loss to follow-up). A comprehensive statistical report will be generated including:

- Primary and secondary endpoint results

- Safety summary
- Subgroup analyses
- Comparison to historical controls
- Bayesian analysis of probability of benefit

12.4 Sample Size Re-estimation

This pilot study has a fixed sample size (N=50). No formal sample size re-estimation will be performed. However, results of this study will inform sample size calculations for a future randomized controlled trial.

13. DATA MANAGEMENT

13.1 Data Collection

13.1.1 Electronic Data Capture

All study data will be captured using REDCap (Research Electronic Data Capture), a secure, web-based application for managing research data. REDCap is:

- Hosted on University of Pittsburgh servers
- HIPAA-compliant with encrypted data transmission and storage
- Access-controlled with role-based permissions
- Audit-trailed (all data entry, modifications, and exports are logged)

13.1.2 Case Report Forms The following electronic CRFs have been created in REDCap:

1. Screening/Eligibility CRF
2. Baseline Demographics CRF
3. Medical History CRF
4. Surgical Details CRF
5. Hospitalization Details CRF
6. Baseline Laboratory Values CRF
7. Day 2 Follow-Up Phone Call CRF
8. Day 31 Follow-Up Phone Call CRF
9. Day 91 Follow-Up Phone Call CRF
10. Adverse Event CRF
11. Serious Adverse Event CRF
12. Medical Record Abstraction CRF
13. Study Completion/Withdrawal CRF

13.1.3 Data Entry

Data will be entered into REDCap by trained research personnel. Source documents include:

- Electronic medical records (UPMC EHR)
- Phone call documentation
- Outside medical records (when obtained)
- Death certificates

- Imaging reports

Data will be entered within 7 days of collection/acquisition.

13.1.4 Data Verification

Key data fields will be verified against source documents by a second research team member. Fields requiring verification:

- Patient identifiers and date of birth
- Eligibility criteria
- Primary outcome (VTE occurrence)
- Serious adverse events (bleeding, death)
- Dates (surgery, discharge, follow-up calls)

Verification will occur for 100% of subjects.

13.2 Data Quality Assurance

13.2.1 Range Checks and Logic Checks

REDCap CRFs include built-in range checks and logic checks to prevent data entry errors:

- Date fields: Must be in valid format and logical sequence
- Numeric fields: Must be within acceptable range (e.g., platelet count 1,000-1,000,000)
- Required fields: Cannot be left blank
- Branching logic: Conditional questions appear only when relevant

13.2.2 Data Review

The research coordinator will perform weekly data quality reviews:

- Check for incomplete CRFs
- Review range check violations
- Check for inconsistencies
- Follow up on missing data

The PI will perform monthly data quality reviews.

13.2.3 Query Resolution

Data queries will be generated for:

- Missing required fields
- Out-of-range values
- Inconsistent data
- Incomplete SAE reports

Queries will be resolved within 7 days.

13.3 Confidentiality

13.3.1 Subject Identifiers

Each enrolled subject will be assigned a unique study ID number (format: SM001, SM002, etc.). The linking key connecting study IDs to patient identifiers (name, MRN,

date of birth) will be stored in a separate password-protected file accessible only to the PI and key study personnel.

13.3.2 Data Storage

- REDCap database: Contains coded data (study ID only, no direct identifiers)
- Linking key: Stored in separate password-protected Excel file on University of Pittsburgh secure server
- Consent forms: Stored in locked file cabinet in PI's office
- Study binders: Printed telephone CRFs Stored in locked file cabinet (contains only coded data)

13.3.3 Data Access

Access to identifiable research data is restricted to:

- Principal Investigator
- Co-Investigators listed on IRB protocol
- Research coordinator

All study team members complete HIPAA training and sign confidentiality agreements.

13.3.4 Data Transmission

If data must be transmitted electronically:

- Use University of Pittsburgh email (encrypted)
- Use password-protected files
- Use de-identified data when possible
- Never include patient identifiers in email subject line or body

13.3.5 Data Retention Per University of Pittsburgh policy and federal regulations:

- All research records will be retained for a minimum of 7 years following study completion
- After the retention period, electronic data will be permanently deleted and paper records will be shredded
- Consent forms will be retained per institutional policy

13.3.6 Data Sharing

De-identified data from this study may be shared with:

- Collaborators for secondary analyses (with appropriate data use agreements)
- The study sponsor for reporting purposes
- Other researchers upon request (after study completion and publication)
- Federal agencies if required by regulation

No identifiable data will be shared outside the study team without specific IRB approval.

14. ETHICAL CONSIDERATIONS

14.1 Informed Consent

14.1.1 Informed Consent Process Informed consent will be obtained from all subjects before any study procedures (except screening under waiver of consent).

The consent process includes:

1. Initial approach and study introduction
2. Provision of written consent form for review
3. Opportunity to discuss with family/caregivers
4. Detailed review of study procedures, risks, benefits, alternatives
5. Assessment of understanding (teach-back method)
6. Verification of decision-making capacity
7. Answering all questions
8. Voluntary signature of consent form

Subjects will be informed that:

- Participation is voluntary
- They may withdraw at any time without penalty
- Their clinical care will not be affected by participation decision
- They will receive a copy of the signed consent form

14.1.2 Consent Timing and Capacity

Consent will be obtained on the day of hospital discharge after spine surgery. To ensure capacity:

- Consent will not be obtained within 12 hours of general anesthesia or procedural sedation. The consenting investigator will verify that the subject is alert, oriented, and able to understand and retain study information prior to proceeding.
- The consenting investigator will verify that the subject is alert, oriented, and able to understand study information
- If there is any doubt about capacity, consent will be deferred or a legally authorized representative may co-sign
- For patients with borderline capacity, family members/caregivers will be involved in the consent discussion

14.1.3 Consent Form

The consent form is written at a 6th-8th grade reading level and includes all required elements per 45 CFR 46.116 and FDA regulations:

- Statement that the study involves research
- Purpose of the research
- Expected duration of participation
- Description of procedures
- Reasonably foreseeable risks
- Potential benefits
- Alternative treatments available
- Confidentiality protections
- Compensation for participation (none)
- Compensation for injury

- Contact information for questions
- Statement that participation is voluntary

The consent form will be reviewed and approved by the University of Pittsburgh IRB.

14.2 IRB Approval

14.2.1 Initial IRB Review

This study will undergo full IRB review by the University of Pittsburgh Institutional Review Board. The following will be submitted:

- Complete protocol
- Informed consent form
- Data collection instruments (REDCap CRFs)
- Grant application
- PI CV and training certificates
- Co-investigator CVs and training certificates

14.2.2 Continuing Review

After initial approval, the study will undergo continuing review at least annually, or more frequently if required by the IRB. Each continuing review will include:

- Updated protocol (if modifications made)
- Progress report (number enrolled, SAEs, protocol deviations)
- Updated consent form (if modifications made)

14.2.3 Protocol Amendments Any substantive changes to the protocol will be submitted to the IRB as an amendment before implementation (except changes to eliminate immediate hazards to subjects).

14.2.4 Scientific Review

This protocol has been reviewed and approved by the UPMC Hillman Cancer Center Protocol Review Committee.

14.3 Risk-Benefit Assessment

14.3.1 Risks to Subjects

The primary risks of this study are:

1. Bleeding complications from apixaban (major bleeding <1%, CRNM bleeding ~3%)
2. Spinal epidural hematoma (risk unknown in this population, estimated <2%)
3. Lack of efficacy (continued VTE risk despite treatment)
4. Inconvenience of phone follow-ups
5. Small risk of confidentiality breach

14.3.2 Potential Benefits to Subjects

Potential benefits include:

- Reduced risk of VTE (expected VTE rate ~5% vs 14.7% historical rate)
- Reduced risk of PE-related morbidity and mortality
- Avoidance of VTE treatment complications

However, there is no guarantee of individual benefit.

14.3.3 Potential Benefits to Society

This study will provide the first prospective evidence on extended VTE prophylaxis after spine surgery for metastatic disease. Results may:

- Inform clinical practice guidelines
- Improve care for approximately 15,000-20,000 patients per year in the U.S.
- Reduce VTE-related morbidity and mortality in this population
- Provide foundation for a larger randomized controlled trial

14.3.4 Risk-Benefit Balance

The IRB will determine that the risks are reasonable in relation to anticipated benefits to subjects and the importance of the knowledge to be gained. This determination is based on:

- High VTE risk (14.7%) in this population
- Well-characterized safety profile of apixaban at this dose
- Potential for meaningful VTE reduction
- Lack of alternative evidence-based prophylaxis strategies
- Careful exclusion of patients at highest bleeding risk
- Structured safety monitoring and stopping rules

14.4 Vulnerable Populations

This study enrolls patients with metastatic cancer, who may be considered vulnerable due to serious illness, limited life expectancy, and dependence on the healthcare system. Additional protections include:

- Clear emphasis during consent that participation is voluntary and will not affect clinical care
- Opportunity to involve family/caregivers in consent decision
- Verification of decision-making capacity before consent
- Right to withdraw at any time without penalty
- Ongoing assessment of continued appropriateness of participation
- Sensitivity to patient's overall clinical situation and prognosis

14.5 Conflict of Interest

14.5.1 Investigator Financial Interests

- The PI and all co-investigators have no financial relationships with manufacturers of anticoagulant medications (Bristol-Myers Squibb, Pfizer, others)
- The PI and co-investigators have no equity interests, patents, or consulting relationships that could be affected by study results
- All investigators have completed University of Pittsburgh Conflict of Interest training and disclosure

14.5.2 Institutional Financial Interests

The University of Pittsburgh has no financial interest related to this research.

14.5.3 Study Sponsor

The study is supported by the Beckwith Institute Frontline Innovation Program. The sponsor has no financial interest in the outcome of the study and will not be involved in data analysis or manuscript preparation.

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16. APPENDICES

APPENDIX A: Schedule of Events (Full Table)
APPENDIX B: ISTH Bleeding Definitions (Detailed)
APPENDIX C: Patient Education Materials - Apixaban Administration Instructions - Bleeding Warning Signs - Emergency Contact Information
APPENDIX D: Data Collection Forms (REDCap CRFs)
APPENDIX E: Informed Consent Form
APPENDIX F: HIPAA Authorization Form
APPENDIX G: Adverse Event Reporting Forms
APPENDIX H: FDA Package Insert for Apixaban (Eliquis)
APPENDIX I: Historical Cohort Characteristics (Detailed)
APPENDIX J: Statistical Analysis Plan (Detailed)
APPENDIX K: Investigator CVs and Training Certifications
APPENDIX L: Grant Application (Beckwith Institute)
APPENDIX M: IRB Approval Letter (To be added after approval)

PROTOCOL SIGNATURE

This protocol represents the complete study plan as of the date below.

Protocol Version: 1.2 Protocol Date: July 13, 2026

James Bayley, MD
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END OF PROTOCOL
