CLINICAL RESEARCH PROTOCOL

PROTOCOL(S) TITLE:	**C**omparison of **A**pixaban ve**r**sus **E**noxaparin for VTE Prevention after Radical Cystectomy (**CARE**)
VERSION NUMBER:	V3
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Abbreviations

AE	Adverse Event
BMI	Body Mass Index
COST	Comprehensive Score for Financial Toxicity
CrCl	Creatinine Clearance
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DOAC	Direct oral anticoagulant
EP	Extended Prophylaxis
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ITT	Intention-To-Treat
NIH	National Institute of Health
NSQIP	National Surgical Quality Improvement Program
PDC	Proportion of Days Covered
PE	Pulmonary Embolism
PI	Principal Investigator
PMAS	PROMIS Medication Adherence Scale
POD	Post operative day
PROMIS	Patient-Reported Outcomes Measurement Information System
PMAS	PROMIS Medication Adherence Scale
RC	Radical Cystectomy
SQH	Subcutaneous heparin
SUO	Society of Urologic Oncology
US	United States
VTE	Venous thromboembolism

STUDY SUMMARY

1.1 Synopsis

Title: Comparison of Apixaban versus Enoxaparin for VTE Prevention after Radical Cystectomy (the CARE trial)

Short Title: Comparison of Apixaban versus Enoxaparin (CARE)

Study Description: Patients who have undergone radical cystectomy for bladder cancer will be randomized to receive a prescription for either enoxaparin or apixaban to self-administer at home until post operative day 30. Their adherence to the assigned medication will be the primary outcome. Comparisons of patient satisfaction, barriers to adherence, and cost will also be collected. The hypothesis is that adherence, satisfaction, and cost will be greater in the apixaban arm.

Objectives:

1. **To compare rates of adherence to discharge on enoxaparin vs apixaban**
    a. Hypothesis: The apixaban group will exhibit non-inferior adherence, as measured by the proportion of prescribed medication accurately administered.
2. **To compare costs of discharge on enoxaparin vs apixaban**
    a. Hypothesis: The median patient out-of-pocket cost, obtained from the institution's outpatient pharmacy data, is expected to be higher in the apixaban group compared to enoxaparin group.
3. **To explore factors contributing to EP adherence**
    a. Hypothesis: it is anticipated that barriers to adherence to enoxaparin will primarily manifest as operational challenges and patient dissatisfaction, while for apixaban, they will predominantly arise from lack of insurance coverage and cost considerations. To evaluate these barriers, a combination of validated questionnaires and novel measures will be employed.
4. **To collect safety and efficacy data on enoxaparin and apixaban**
    a. Considering that our study size will limit statistical power to detect risk reduction in venous thromboembolism (VTE) and/or bleeding events in either enoxaparin or apixaban, we will instead closely monitor and assess VTE and bleeding events in both treatment arms to contribute to existing studies for possible meta-analysis. This will be achieved

through the implementation of screening questions at each visit.

Primary Endpoint:

To address our primary objective, adherence, the primary endpoint will be measured as the proportion of days covered (PDC), ie the proportion of days between discharge and post operative day 30 during which the participant took their anticoagulant as prescribed.

Secondary Endpoints:

To address our secondary objective of comparing risk factors for adherence/non-adherence, secondary endpoints include:

1. National Institute of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Medication Adherence Scale (PMAS) – a validated, nine-item, patient-reported measure of medication adherence[1]
2. Patient Satisfaction – a series of independent questions that investigate barriers to adherence specific to apixaban or enoxaparin

To address our secondary objective of comparing cost, secondary endpoints also include:

3. Patient out of pocket cost for anticoagulant prescription (in dollars)
4. COST-FACIT, a 12-item survey developed and validated in the cancer population for assessing patient-reported financial distress due to healthcare costs[2]

Study Population:

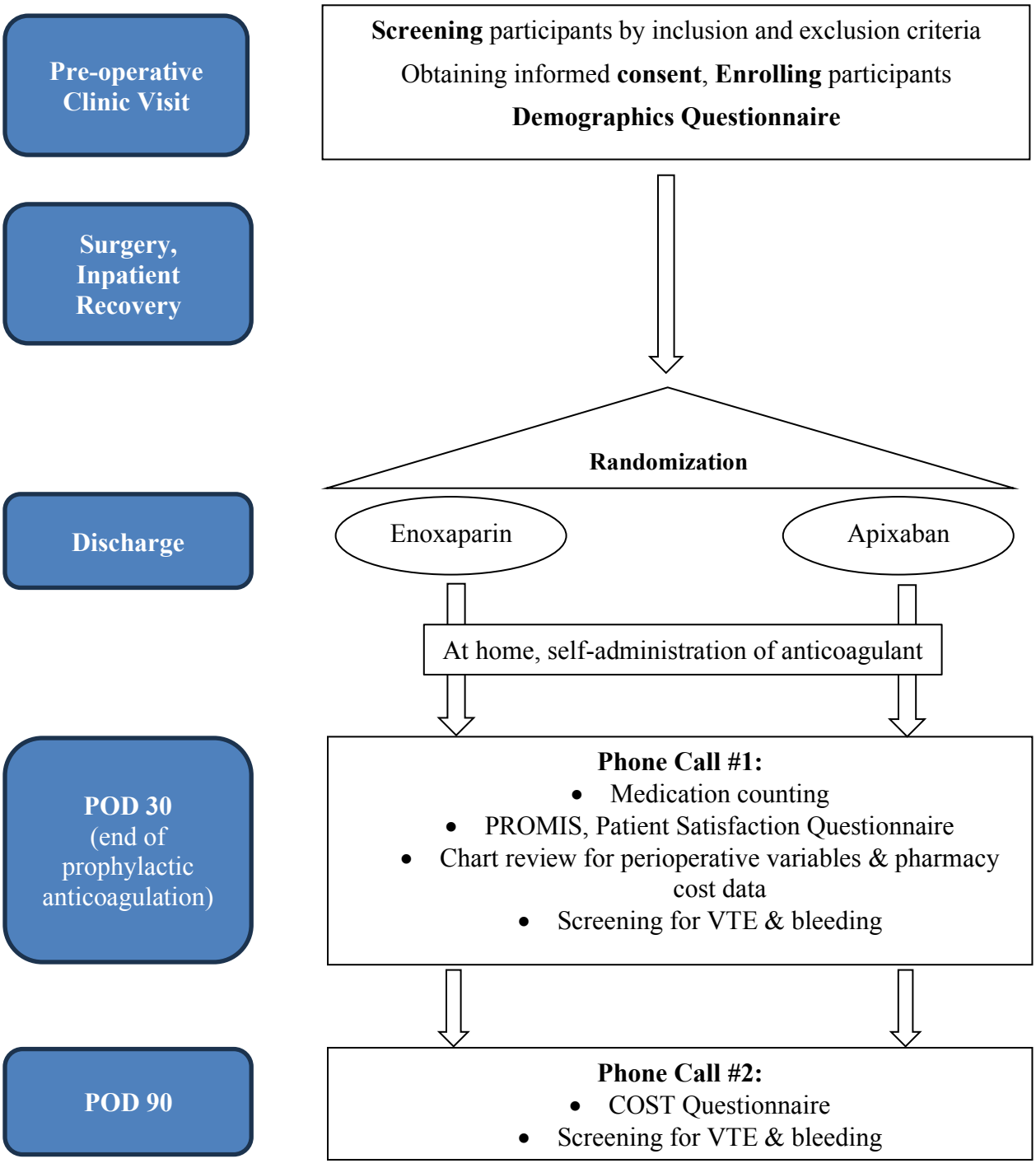
Inclusion Criteria: All patients undergoing RC with urinary diversion and pelvic lymph node dissection for urothelial bladder cancer (any T stage, N0-1, M0) at the participating institutions.

Exclusion Criteria:

1. Preoperative use of a therapeutic dose of anticoagulant (this notably does *not* exclude patients taking antiplatelet agents)
2. Failure to undergo radical cystectomy with concurrent urinary diversion and pelvic lymph node dissection
3. Failure to be discharged by POD14
4. Failure to be discharged on prophylactic enoxaparin or apixaban.
5. Any medical condition which precludes treatment with *either* enoxaparin *or* apixaban (including dialysis,hemophilia, or any other bleeding diathesis)
6. Inability to communicate over the phone in English

	Due to the natural history of bladder cancer, the expected population will be mixed in age, race, gender, and general health status, though likely to be majority white males between the ages of 50-80 in generally good health status (enough that they are safe to undergo RC, which is a major surgery). Target sample size is 108 participants
Enrolling Sites:	Hospital of the University of Pennsylvania (HUP), Philadelphia, PA Vanderbilt University Medical Center, Nashville, TN
Description of Study Intervention:	**Enoxaparin and apixaban are both established treatments in clinical practice and considered acceptable standards of care**. However, enoxaparin has historically been utilized for extended prophylaxis prior to the availability of apixaban and is slightly more commonly prescribed. Hence, in this study, randomization to apixaban will be considered the intervention for convention. Enoxaparin is taken by subcutaneous injection 40 mg once daily for VTE prophylaxis. Apixaban is taken orally as a tablet at a 2.5 mg twice daily for VTE prophylaxis.
Study Duration:	30 months
Participant Duration:	From preoperative clinic visit to 90 days postop, approximately 4 months

1.2 Schema


Pre-operative Clinic Visit
Screening participants by inclusion and exclusion criteria
Obtaining informed consent, Enrolling participants
Demographics Questionnaire
Surgery, Inpatient Recovery
Randomization
Discharge
Enoxaparin
Apixaban
At home, self-administration of anticoagulant
POD 30 (end of prophylactic anticoagulation)
Phone Call #1:
Medication counting
PROMIS, Patient Satisfaction Questionnaire
Chart review for perioperative variables & pharmacy cost data
Screening for VTE & bleeding
POD 90
Phone Call #2:
COST Questionnaire
Screening for VTE & bleeding

2 INTRODUCTION AND BACKGROUND

2.1 Study Rationale

Venous thromboembolism (VTE), including both deep venous thrombosis (DVT) and pulmonary embolism (PE), after radical cystectomy (RC) constitutes a significant burden on bladder cancer patients in terms of morbidity, mortality, and cost. PE is one of the most common causes of perioperative mortality after RC, reported to be 16% in one study.[3] Patients diagnosed with DVT or PE require at least six months of anticoagulation and treatment, resulting in burdensome medication use and followup appointments. The annual per-patient cost of DVT or PE has been reported as high as $3,000 or $6,000, respectively.[4] Prior analyses of large datasets suggest the incidence of symptomatic VTE ranges from 2-12% in the first 30 days after surgery,[5–12] and data confirm the risk is sustained after hospital discharge.[5,9,10,12]

Growing recognition of this burden led to the practice of extending the period of pharmacologic prophylaxis against VTE beyond just the patient's inpatient stay so that the patient continues prophylaxis until the 30th postoperative day (POD). This practice is well established and codified into many surgical oncologic guidelines, both urologic and others. The data supporting the practice in oncologic surgery populations are quite robust; a recent Cochrane Review of seven randomized, controlled trials of patients postop from abdominal and pelvic oncologic operations shows the rate of VTE was reduced from 13% in the non-prophylaxis group to 5.3% in the group receiving the blood thinner enoxaparin for 28 days after surgery.[13]

Regarding the bladder cancer population and RC specifically, a single institution study of over 400 patients showed a decrease in VTE rate from 12% to 5% after instituting the practice of 28 days of enoxaparin after discharge,[14] and a more recent study showed an even bigger decrease from 17.6% to 5.06% in the 90 days after discharge.[15] The European Association of Urology (EAU) has thus adopted a recommendation stating, "the optimal duration of pharmacological prophylaxis is approximately four weeks post-surgery."[16]

In the face of the mounting evidence and these emerging guidelines, the practice of extended VTE prophylaxis has rapidly expanded in the past several years and become standard of care. An analysis of the Optum database of prescription data suggests the practice of prescribing enoxaparin after discharge after RC increased from only 9% of cases in 2012 to 26% in 2017.[17] Even more recently, a 2020 survey of 121 physician members of the Society of Urologic Oncology (SUO) reported 80% endorsed the use of extended prophylaxis (EP) for this duration.[18]

There are still several barriers that exist to the full adoption of discharge on enoxaparin injections. In addition to the eligibility restrictions based on renal function, patients continue to face significant operational and quality of life barriers, including issues related to insurance coverage, cost, as well as the pain and discomfort experienced during self-injections. In the described SUO survey, half of providers that prescribe EP report experiencing issues with lack of

insurance coverage for enoxaparin injections (38%), inability of patients to afford the medication (51%), and need to perform cumbersome additional insurance authorization processes (44%). Approximately 20% report issues with patient adherence and refusal to perform the enoxaparin injections. The providers who elected not to prescribe EP correspondingly cited these as reasons they elected not to use it.[19] Similar reports exist in non-urologic cancer surgery; among those surgeons who were noncompliant with EP guidelines for pancreatic and hepatobiliary surgeries, the most significant barriers reported were "drug cost," "subcutaneous injections, and "logistical challenges of prescribing."[20]

Direct Oral Anticoagulants (DOACs), specifically apixaban, have recently emerged as a viable option for providing pharmacologic VTE prophylaxis to patients after discharge while avoiding some of the persistent issues encountered with discharge on enoxaparin. Gynecologic oncologists have been early adopters of this practice and their pelvic cancer surgeries offer a reasonable comparator to RC. In a recent trial, 400 women undergoing gynecologic cancer surgery were randomized to 28 days of either prophylactic enoxaparin or apixaban with results showing there were no differences between groups for rates of major bleeding or venous thromboembolic events but patients in the apixaban group reported increased ease and decreased pain associated with taking the medication.[21] There is even stronger data supporting the efficacy of apixaban as compared to enoxaparin in the orthopedic field, with a randomized trial of over 3,000 patients showing a 15% VTE rate using apixaban as EP compared to 24% using enoxaparin.[22]

2.2 Previous Literature

In the urologic field, there have been only a handful of exceedingly small, retrospective studies investigating the feasibility of using apixaban after discharge.[23–25] Urologists from the University of Missouri and St. Louis University initiated a quality improvement pathway for recovery after RC which included prescribing apixaban at discharge until POD 28. Their retrospective review of 72 patients who completed the apixaban protocol showed no increase in rates of DVT, major bleeding, or other complications compared to their historical rates.[25] The Mayo clinic in Arizona similarly made an institutional change to using a DOAC rather than enoxaparin as EP in 2019 and performed a retrospective comparison of 46 patients who received a DOAC, 55 patients who received enoxaparin and 556 patients who received no EP (from either before or after 2019). Their results show VTE rates of 0%, 3.6% and 7.2% in the cohorts who received a DOAC, enoxaparin, and no VTE prophylaxis, respectively (p=0.11). They also indicate no significant difference in GI bleeding among the three groups.[23] Looking specifically at patients who underwent robot-assisted radical cystectomy at another academic center, Ortiz et al. perform a retrospective comparison enoxaparin vs DOACs following an institutional change to using DOACs. Of 66 patients included in their review, their data show DVT rates of 3/37 patients in the enoxaparin arm vs 1/29 in the DOAC arm; a difference which was not statistically

significant. They also show no statistical difference in postoperative complication rates including ED returns, readmissions, bleeding events, or wound complications.[24,25]

The largest of these types of retrospective cohort studies was performed by Westerman et al. at MD Anderson in 2021. Similarly, it is a retrospective comparison of the outcomes following an institutional change from the use of enoxaparin to the use of apixaban; Westerman et al. capture 145 patients in each phase. Their results suggest a possibly improved DVT rate on apixaban (0% vs 3.1%) following the switch, as well as fewer compliance "events" (0% with apixaban vs 33.5% with enoxaparin).[26] Notably, this was not a randomized study, not all patients who were discharged on prophylaxis had undergone RC, and not all patients who underwent RC were discharged on prophylaxis; apixaban was simply used in urologic cancer cases where surgeon discretion would have led to discharge on enoxaparin prophylaxis.

In summary, the clinical benefit of extended prophylaxis in reducing venous thromboembolism (VTE) immediately after major abdominal oncologic surgery is evident. The use of DOACs as a substitute for enoxaparin has been extensively studied in non-urologic cancer patients, but its adoption by urologic cancer surgeons is still in the early stages. While several small retrospective reports have been published, demonstrating the safety outcomes of switching to DOACs as EP, the potential advantages of using DOACs to mitigate the issues associated with enoxaparin self-injection and enhance patient adherence and accessibility to these medications remain unexplored.

2.3 Preliminary Institutional Results

Given the earlier data suggesting barriers to adoption include cost, we sought to assess the state of prescription costs at our institution and determine how likely this is to pose a barrier to patient adherence. We reviewed our institution's outpatient pharmacy data from July to December of 2022, including the copays that patients being discharged on prophylactic dose apixaban and enoxaparin face at our institution as well as difficulties encountered with prior authorizations. Data suggest that copays may vary from as low as $0 to >$100, and that copays are much more likely to be increased with apixaban (Table 1). Review of prior authorizations show that a substantial number of prior authorizations were submitted, and in particular that denial of these prior authorizations and insurance coverage may pose a problem for both medications, in particular apixaban (Table 2).

Table 1. Patient copays for Enoxaparin and Apixaban

Lovenox PX (30mg & 40mg QD)	
Copay ($)	Count
0	103
0-20	108
21-50	27
51-100	14
>100	17
Total	269

Apixaban PX (2.5mg BID)	
Copay ($)	Count
0	15
0-20	14
21-50	11
51-100	3
>100	4
Total	47

Table 2. Outcomes of prior authorizations submitted for Enoxaparin and Apixaban

Prior Authorizations			
Medication	Approved	Denied	Total
Apixaban	32	9	41
Lovenox	19	2	21

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare rates of adherence to discharge on enoxaparin vs apixaban	Proportion of days covered (PDC). This will be calculated based on the size of prescription the patient was provided, day of surgery, day of discharge, and how many pills/syringes are remaining at POD30.	This is an objective and quantitative way to measure adherence.
Secondary		
To explore possible reasons for adherence vs non adherence	PROMIS Medication Adherence Scale: a nine-item questionnaire[26,27]	This is a validated measure of medication adherence that focuses on the possible reasons for non-adherence
	Participant satisfaction	Participants will answer questions specific to the use of enoxaparin and apixaban at home after RC. These questions were selected based on the clinical experience of the PIs as well as other studies that have examined adherence to enoxaparin and apixaban[21,27,28]
	COST-FACIT: a 12-item questionnaire[2]	This is a questionnaire that was developed and validated in the cancer population for assessing patient-reported financial distress due to healthcare costs. This questionnaire adds a patient reported component, as simple cost data does not capture how burdensome that cost is to each specific patient
To compare the cost of enoxaparin vs apixaban	Out of pocket cost of prescription for anticoagulant, in dollars	This provides objective measure of the cost comparison between enoxaparin and apixaban. This data combined with adherence data may allow providers to determine the most cost effective option.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary		
To collect mefficacy and safety data regarding both forms of prophylaxis	Rate of VTE, either PE or DVT Rate of bleeding events, classified as major, clinically relevant nonmajor, or nonmajor.	While data suggest VTE rates are comparable between enoxaparin and apixaban in both non-urologic and urologic studies, the urologic studies are in small populations. We therefore plan to track VTE and bleeding as outcomes to continue contributing to the pool of data. These outcomes would likely have been measured even if they were not outcomes as part of safety monitoring.

4 STUDY DESIGN

This is a pragmatic, multi-site, randomized, controlled trial comparing two anticoagulant medications, enoxaparin and apixaban, when given to bladder cancer patients as VTE prophylaxis after RC.

The primary objective of the study is to assess participant adherence to the at-home anticoagulation regimen. Other objectives include participant satisfaction and cost burden. At 30 days postop study team members will call participants to assess the primary endpoint of adherence as well as secondary endpoints of cost and patient satisfaction. At 90 days the participants will receive another phone call to complete one additional questionnaire assessing financial burden since surgery. While both drugs are considered standard of care for EP after RC, apixaban is considered the intervention arm due to its more recent introduction and use at this institution. The study is powered to detect if adherence to apixaban is noninferior to enoxaparin. If this criterion is met the study will also test for the superiority of apixaban.

4.1 Minimizing Bias

Patients will be randomized to a prescription for one of the two anticoagulants at the time of postoperative discharge, and instructed to continue the medication until POD30. Randomization will be performed in a simple 1:1 fashion.

The randomization will be non-blinded. Given that this trial aims to explore the real experience of patients on these medications, blinding and placebo would actually detract from the important clinical context and understanding that participants have. Furthermore, enoxaparin and apixaban have different routes of administration (enoxaparin is injectable and apixaban is oral) which makes blinding and placebo infeasible. Blinding of the investigators is not necessary given the outcomes are patient reported surveys and pill/vial counts. Bias will be sufficiently reduced by randomization.

The University of Pennsylvania will serve as the primary site, and Vanderbilt University Medical Center as a second site. The addition of a second site will also introduce variety into the study population and strengthen its applicability.

4.2 Risk/Benefit Assessment

Enoxaparin and apixaban are both FDA approved in the context of VTE prophylaxis and prescribed after cystectomy as standard of care (SOC). The benefits of postoperative anticoagulation for reducing rates of VTE have been repeatedly demonstrated in the literature and are included in society guidelines (see Section 2.1). The most relevant clinical risk with either medication is bleeding, which is a low risk at the prophylactic dose utilized in this study.

The most important point in assessing risk/benefit in this study is that the standard of care includes extended prophylaxis (EP) postoperatively. Thus, **participants will neither gain clinical benefit nor avoid clinical risk by participating because they would have been given EP regardless.** The selection of one of these two anticoagulants is currently determined by

prescriber preference in clinical practice. Enoxaparin is currently the more commonly prescribed at this institution so is considered the "control" group for notation purposes in this trial.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Able to communicate in English over the phone
4. Male or female, age >18 years
5. Diagnosed with biopsy-proven, urothelial cell carcinoma (any T stage, N0-1, M0) with plan for radical cystectomy with urinary diversion and concurrent pelvic lymph node dissection as treatment

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Preoperative use of a therapeutic dose of anticoagulant (this notably does *not* exclude patients taking antiplatelet agents)
2. Failure to undergo radical cystectomy with concurrent urinary diversion and pelvic lymph node dissection
3. Failure to be discharged by POD14
4. Failure to receive a script for enoxaparin or apixaban.
5. Any medical condition which precludes treatment with *either* enoxaparin *or* apixaban (including dialysis, hemophilia or any other bleeding diathesis)

5.3 Recruitment

The University of Pennsylvania historically performs ~70 cystectomies per year. Vanderbilt University Medical Center performs ~90 per year. To achieve the target analysis group of 90 patients we plan to enroll 108 (see section 9.3.1). Thus the planned recruitment/enrollment period is approximately 12 months.

Recruitment will take place in outpatient offices. We will review the medical charts of patients seeing our Urologic oncology surgeons a week ahead of time and flag charts that suggest a radical cystectomy may be an indicated therapy for a patient. Staff will plan to be available on these days to screen and enroll as able.

The treating physician will discuss post-operative extended prophylaxis (EP) with anticoagulants with the patient during their visit because it is standard of care. Within this context the treating physician will introduce the option to participate in the trial and undergo randomization between forms of EP, however it will be made clear to the potential participant that they will receive standard of care EP regardless of their choice to participate or not.

After the visit, further discussion of the trial and screening will be performed by trial staff other than the treating physician, and participants will be allowed to think about their decision after the initial discussion and enroll at a later date (as long as they enroll prior to undergoing surgery). Both of these features will help further mitigate any undue pressure patients may feel. If a patient cannot be approached in person or decides they would like to think longer about their decision to participate, a member of the research team will contact them by phone and complete the remaining enrollment process over the phone and electronically.

6 STUDY INTERVENTION

Both enoxaparin and apixaban are FDA approved in the setting of VTE prophylaxis and considered standard of care for EP after radical cystectomy. Study personnel will not be directly providing or administering either drug. Rather, *the study intervention is the randomization to receive a prescription (with standard clinical counseling) for either of the two forms of prophylaxis*. The participant will then be responsible for filling the prescription at their own cost and self-administering the anticoagulant, as would be standard of care after a radical cystectomy. The anticoagulants will be prescribed according to the clinical standard of care: 40 mg injected subcutaneously once daily for enoxaparin and 2.5 mg tablet taken orally twice daily for apixaban. Doses may be reduced in increased based on the patient's medical comorbidity profile (for example weight and CrCl) according to standard prescribing practices. Regardless of the time of day of discharge, participants will be instructed to start self-administering the medication the day after discharge, and continue through post-op day 30.

Participants who fail to receive a prescription for either anticoagulant will be considered not to have received the study intervention. Participants who receive the prescription but report poor compliance with the prescription have still received the study intervention; their poor compliance is tracked as the primary outcome of the study.

7 STUDY ASSESSMENTS

At the time of enrollment, participants will be offered to complete the Demographics questionnaire either in person (if applicable), via phone (if applicable), or via a secure REDCap link emailed to them.

Participants will be contacted via phone on POD30 and POD90. During the phone call, participants will be given the option to receive an email with a secure link to REDCap to complete the majority of the study visit electronically (PMAS, Patient Satisfaction, and COST

questionnaires). Medication counting and screening for adverse events including VTE and bleeding must be done over the phone rather than via emailed link.

Study assessments will be conducted by staff other than the treating physician, and staff members will clearly state the contact is part of the research study, not part of routine clinical care.

7.1 Adherence & Satisfaction Assessments

The following assessments will be made to assess the adherence and satisfaction with anticoagulants after cystectomy (corresponding to primary and secondary objectives in section 3):

1. **Medication counting–** study personnel will assist with medication counting over the phone. This involves the participant counting the pills/vials of medication they have remaining and then the study personnel will use the date of surgery, date of discharge, and size of prescription found in the medical record to calculate the **proportion of days covered (PDC)**. PDC is the primary endpoint of the study and is the most objective measure of adherence.
2. National Institute of Health (NIH) Patient-Reported Outcomes Measurement Information System **(PROMIS) Medication Adherence Scale (PMAS)**[29,30] – this questionnaire is a validated, nine-item, patient-reported measure of medication adherence that can be either administered by study personnel over the phone or filled out directly in RedCap by study participants who elect to have a secure weblink emailed to them.
3. **Patient Satisfaction** – study personnel will ask a series of independent questions over the phone or participants will answer them directly in RedCap if they elect to have a secure weblink emailed to them. These questions elucidate possible reasons for compliance/noncompliance that are hypothesized specifically to apply to enoxaparin and apixaban.

7.2 Cost Assessments

The following assessments will be made to assess the cost of anticoagulants when used as EP (corresponding to secondary objectives in section 3).

1. **COST-FACIT** – this is a 12-item questionnaire developed and validated in the cancer population for assessing patient-reported financial distress due to healthcare costs that can be either administered by study personnel over the phone or filled out directly in RedCap by study participants who elect to have a secure weblink emailed to them.
2. The total cost, amount paid by insurance, and patient out of pocket cost for each anticoagulant (in dollars) will be tracked by the inpatient pharmacy. This is collected via electronic review of pharmacy records.

7.3 Assessing Covariates

1. **Demographics Questionnaire –** this questionnaire is administered by study personnel either in person, over the phone, or filled out directly in RedCap by study participants who elect to have a secure weblink emailed to them. Some chart review may be performed to assist in completion. It will collect variables to help evaluate what sociodemographic covariates may be influencing study endpoints.
    a. The Demographics Questionnaire we include the **modified, 5-item Frailty Index.**[29] Initially developed a an 11-item index, the Frailty Index was developed using NSQIP comorbidities and then shortened to a 5-item index that has been shown to predict complications, discharge destination, and healthcare utilization after radical cystectomy.[30,31]
2. In addition to these discrete questionnaires, **chart review** will be performed ascertain what **perioperative variables** may be influencing study endpoints:
    a. Length of surgery
    b. Surgical approach (robotic vs open)
    c. Type of diversion (ileal conduit, catheterizable channel, or neobladder)
    d. Number of blood transfusions both intraop and periop (in units)
    e. Length of stay (in days)

7.4 Drug Efficacy & Safety Assessments

In order to achieve the tertiary objective of collecting data regarding the efficacy and safety of both enoxaparin and apixaban when used as EP in the setting of radical cystectomy, we will directly enquire about instances of VTE and instances of bleeding. Screening questions for VTE and bleeding will be performed by study personnel and any positive screen will trigger review by one of the investigators, including review of the participant's medical record for results of imaging, labwork, notes from ED visits or inpatient admissions, or any other information deemed necessary by the investigator to confirm presence of VTE or bleeding and describe the outcome. This review will be conducted in accordance with HIPPA regulation. Review of the VTE or bleeding event will be performed for study documentation purposes; participants will be referred to their treating clinician for management of the VTE or bleeding, or if deemed necessary by the PI, to the emergency department for expedited care and their treating clinician notified of this for continued management.

7.4.1 *Assessing VTE*

VTE will be categorized as DVT, PE, or both. To asses for VTE, all participants will be directly asked if they have been diagnosed with a blood clot. A positive screen will be reported to the investigators who will review the event as described above,

Development of VTE may result in the patient being discontinued from the study intervention (because they will likely no longer be on prophylactic dose of anticoagulant, but rather therapeutic dose) but not discontinuation from the study.

7.4.2 *Assessing Bleeding*

Bleeding events will be categorized as Major, Clinically-Relevant Non-Major (CRNM), and Minor. Major events and CRNM are defined according to the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee of Scientific and Standardization Committee.[32,33] Minor bleeding is defined as clinically overt bleeding that does not meet criteria for Major or CRNM bleeding.

To assess for Major and CRNM bleeding, participants will be directly asked if they have had bleeding that resulted in presentation to ED, inpatient admission, transfusion, or procedural intervention. To assess for Minor bleeding (or bleeding that is Major/CRNM but not yet diagnosed) participants will be asked about bruising or any other bothersome bleeding. All positive screens for bleeding events will be reviewed by a trial investigator to ensure appropriate clinical classification as Major, CRNM, or Minor. A positive screen will be reported to the investigators who will review the event as described above

8 SCREEN FAILURE, DISCONTINUATION, AND CROSSOVER

8.1 Screen Failures

Screen failures are defined as participants who agree to participate in the clinical trial but do not ultimately enroll. In order to comply with the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, all potential participants who are screen failures will complete a demographics form and the reason for their screen failure will be documented.

Participants who are screen failures due to a medical contraindication to enoxaparin or apixaban which then improves to meet the trial standard may be rescreened and will be assigned the same participant number as for the initial screening.

8.2 Discontinuation of Study Intervention, Discontinuation from Study

Prophylactic anticoagulation is standard of care after RC and therefore the decision to stop prophylaxis should be situated within a discussion with the treating clinician. The following are anticipated reasons participants may be told to discontinue study intervention (ie stop their anticoagulant) by their treating clinician:

- Development of blood clot. This would require discontinuation of prophylactic dose in favor of therapeutic dose and may involve switching anticoagulant type
- Development of bleeding event
- Development of an adverse event possibly related to the anticoagulant

- Development of a serious adverse event that would make prophylactic anticoagulation contraindicated

If study personnel discover any of these occurrences during study visits and they are not known already to the treating clinician, study personnel will refer the participant to their treating clinician for management, which may include consideration of discontinuation of the anticoagulant.

Study personnel will screen for discontinuation of the study intervention (ie discontinuation of the assigned anticoagulant) that has already occurred at the beginning of the POD30 and POD90 telephone calls. Any instances of study discontinuation will be brought to the attention of the PI and at the discretion of the PI participants who must discontinue the study intervention may remain in the study and complete portions of study visits depending on their reason for anticoagulant discontinuation and length of time they were following study protocol.

Participants may alternatively be discontinued completely from the study for the following reasons:

- Failure to undergo radical cystectomy and pelvic lymph node dissection
- Failure to be discharged on prophylactic anticoagulant
- Failure to be discharged by POD14
- Lost to Follow Up, defined as failing to complete the study visit despite three attempts to contact the participant via phone and/or email
- Participant request; participants are free to withdraw at any time

Any study discontinuation or discontinuation of the study intervention will be documented, including the date and reason for discontinuation. All instances will be reviewed by PI.. Participants who are discontinued will not be replaced.

8.3 Crossover Between Study Arms

If a participant has or develops a contraindication to the specific drug they have been randomized to receive prior to discharge on EP (ie prior to initiation of the study intervention), they will be considered for crossover to the other arm and, if there is no contraindication to the other drug, can be switched to that arm. These instances and reasons for crossover will be documented. Crossover in this way will be allowed so that patients are not deprived of the standard of care anticoagulation after RC for their participation in the study and to better mimic the current prescribing patterns in which the drugs are frequently substituted for each other. Potential bias from allowing crossover is expected to be minimal as there is not a strongly plausible link between the contraindications to enoxaparin or apixaban and adherence to enoxaparin or apixaban. Furthermore, the contraindications to enoxaparin and apixaban are mostly quite rare; the only anticipated contraindication will be creatinine clearance (CrCl) <30 for enoxaparin. Any other possible indication for crossover will be reviewed by PI. Patients who crossover should still complete the study visits and both an intention to treat (ITT) and per-protocol (PP) analyses will be completed.

9 STATISTICAL CONSIDERATIONS

9.1 General Approach

Continuous variables will be presented as means with standard deviation or median with interquartile range. All statistical tests of significance will be two-sided with alpha level 0.05. Stata will be used for all statistical analysis.

9.2 Baseline Descriptive Statistics

Participants in the two study arms will be compared on their baseline demographics characteristics, collected from the Demographics Questionnaire, and on their operative characteristics, collected by chart review. Inferential statistics will be used to test for significant differences across study arms at baseline. To conduct these statistical tests, we will apply either standard t-tests for continuous measures or difference in proportion tests for binary measures.

9.3 Analysis of the Primary Endpoint

The primary objective of this study is to compare drug adherence between the two study arms, and the corresponding primary endpoint of the study is the proportion of days at home during which the participant took the prescribed anticoagulant. This is defined as the proportion of days covered (PDC).

PDC = number of days of anticoagulant actually taken /
number of days of anticoagulant supposed to take

Number of days of anticoagulant actually taken is determined during the POD 30 phone call by asking the participant how many pills/vials they have remaining and then subtracting that from the size of the prescription they were given. Number of days of anticoagulant supposed to take is calculated by subtracting the number of days postop the patient was discharged from 30.

PDC will be compared between the two groups using a **non-inferiority trial design** with difference in proportions test with the following hypothesis:

H_0: Apixaban is inferior to Enoxaparin in terms of the average PDC response.

H_A: Apixaban is non-inferior to Enoxaparin in terms of the average PDC response.

9.3.1 *Sample Size Calculation*

Prior studies suggest the at-home adherence to daily lovenox regimen is around 85%.[21,28,34,35] Assuming a baseline PDC in the control group of 85% and non-inferiority margin of 15%, a sample size of 45 subjects per arm, 90 subjects total, will provide 80% power to detect non-inferiority at a one-sided significance level of 0.05..[36]

9.4 Analysis of Secondary Endpoints

The following secondary endpoints will be assessed to further characterize adherence and also related elements of satisfaction and cost, though analyses of these related elements are not dependent on findings of the primary endpoint.

1. A binary measure of adherence: adherent vs non-adherent. Adherent is defined as taking *all* intended anticoagulant. Adherence in this definition will be compared using a test of proportions (proportion of patients in one study arm that were "adherent" vs proportion of patients in the other arm that were "adherent") within the ITT and population.
2. Cost of the medication. There are several measures of cost that will be studied as endpoints, including overall medication cost, cost paid by insurance, and most importantly participant out of pocket cost. Cost will be measured in dollars and reported as median and as mean depending on the presence of outliers. This will be collected from pharmacy review of prescriptions. Cost will be compared using a rank sum test.
3. Scores on the two validated questionnaires given: PROMIS and COST. These validated questionnaires both have scoring systems and a t test of the average score of participants in each arm will be compared (ie average score on COST for participants in apixaban arm vs average score on COST for participants in enoxaparin arm). A rank sum test will be used if distributions have outliers.

9.5 Exploratory Analysis

Analysis of other factors influencing adherence to at home anticoagulation in this population are considered exploratory. To explore what factors other than type of anticoagulant may be impacting adherence, we plan to perform a logistic regression with the outcome variable of PDC. Covariates will include the following: age, gender, ethnicity, marital status, living situation, occupational status, education level, annual household income, insurance status, history of prior blood clot, number of daily medications, discharge destination, study arm, and items from the Satisfaction Questionnaire. Univariate regression will be performed first followed by multivariate regression including all variables that were significantly associated on univariate regression.

A second exploratory analysis will be comparing elements of the novel satisfaction questionnaire trial between the apixaban and enoxaparin arms. Items from this questionnaire may be compared by presenting descriptive statistics without formal tests for statistical significance in order to explore how patient satisfaction varies between the study arms and allow future physicians to give anticipatory guidance.

9.6 Analysis of Safety Endpoints

Given the well-established safety profile of both drugs and their use as SOC after cystectomy there is no formal safety endpoint for this study. However, both bleeding and VTE events will be solicited and tracked (see section 7) for safety analysis. DVT, PE, and a composite

outcome of the two will be compared between the two study arms using a test of proportions. For bleeding events, medical review of the chart by an investigator will determine if the event is Major, Clinically Relevant Non-Major (CRNM), or Minor (see section 7) and these three outcomes will be compared between the two groups as well as a composite outcome of Non-Minor Bleeding (Major and CRNM) using test of proportions.

These as well as any other adverse events will be graded (see section 7) and presented in a descriptive way with any further detail deemed clinically relevant by the PI (including but not limited to the treatment and outcome of the AE) included.

9.7 Populations for Analyses

The analysis of primary endpoint, PDC, as well as analyses comparing the results of the questionnaires will be conducted using an Intention-to-Treat (ITT) Dataset consisting of all randomized participants. We expect minimal crossover after randomization however if there is significant crossover we would also perform the analysis in an "As Treated" (AT) dataset consisting of participants categorized to the drug they ultimately received after crossover. Cost analyses will be performed using a dataset of all prescriptions (there may be more than one prescription per participant if there is crossover between study arms, though again this is expected to be minimal). Safety analyses will be performed in the ITT dataset as well as in participants who meet criteria for "adherent" to their anticoagulant (as defined above in section 9.4). Missing data will be assumed random and discarded from all analyses; missing data is expected to be low as there are only two study visits.

10 OPERATIONAL CONSIDERATIONS

10.1 Study Personnel

The study personnel will consist of the PIs, sub-investigators, research coordinators, pharmacists, statisticians, research nurses, and medical students from both sites.

10.2 Informed Consent Process

Informed consent will be administered by members of the study team. To ensure privacy, the screening, enrollment, and informed consent process will take place in a patient exam room, study investigator/team member's private office, other private clinical space, or over the phone if the patient cannot be met in person immediately following their preoperative visit. This will ensure privacy during open discussion.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Questions will be solicited and answered.

Since we believe that this study represents no more than minimal risk to the subjects, there will be no required waiting period between informed consent, enrollment, and participation

in the study. Since the intervention of the study involves only randomization between two standard of care drugs and completion of questionnaires, we believe that there is minimal risk of coercion or undue influence. Participants will however have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will also be allowed to delay signing consent form to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The informed consent process will be conducted, documented, and the form signed, before the participant undergoes any study-specific procedures.

Consent will be given electronically using the secure platform REDCap for participants who enroll in person after their pre-op visit. Participants will have time to review the electronic consent form on the computer prior to signing electronically. They will receive a copy of their signed consent form. Some participants may be contacted via phone for screening and enrollment after their visit and will be emailed a link to REDCap to provide electronic consent and receive a signed copy of their consent form. For participants who are not able to give electronic consent a paper copy will be used.

10.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by all study personnel. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI and IRB.

10.3.1 *Data Collection, Handling, and Management*

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source data include data from the questionnaires (which includes demographic information as well as participant reported outcomes) as well as data abstracted from the medical record and hospital pharmacy. Data will be stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. Data from the questionnaires will be captured directly through the HIPAA complaint REDCap service housed at the University of Pennsylvania (http://www.med.upenn.edu/scrcm/redcap.html), either by the participant directly entering their responses into REDCap or by study personnel completing a phone interview and recording participant responses directly into REDCap. Additional data captured by review of epic medical chart and pharmacy records will also be entered directly into REDCap by study personnel. All research activities including chart review and phone interviews will be conducted in as private a setting as possible.

All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will

be password protectedand only study team members will have access to the REDCap database. Participants are given a unique number in REDCap for linkage. If data is shared with outside researchers, data will be de-identified by standard REDCap procedure for removing personal identifiers.

If plans to add additional sites arise, a Data Use Agreement will be executed between the University of Pennsylvania and any participating sites. All outside sites will be given access to the site-specific REDCap data access group. Participating sites will be asked to share data with the central site investigator for data collection and analysis.

10.3.2 *Protected Health Information*

We plan to collect he following PHI from subjects:

1. Name
2. Birth date
3. Address
4. Telephone number
5. Electronic mail addresses
6. Medical record numbers
7. Medical comorbidities
8. Sex assigned at birth, gender

10.3.3 *Study Records Retention and Future Use of Data*

All study records will be retained in REDCap for future use in research projects conducted within the division of Urology. This may include sub-analyses to inform possible future projects, or use of this trial as a pilot to be expanded into a larger study with greater power to analyze some of the secondary, tertiary, and safety/efficacy outcomes. Any future use will be limited to within the Penn division of Urology. Subjects will have the option to elect out of the storage of the PHI elements for future use.

10.4 Adverse Events

The medical complication rate after radical cystectomy is relatively high; it has been reported around 60% for all complications and 30% for Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 complications in the first 90 days postoperatively.[37] Therefore the vast majority of adverse events in this study are expected and have no plausible relation to VTE prophylaxis with either enoxaparin or apixaban. The known risks of enoxaparin and lovenox are defined on the drug labels

The study goal is to evaluate VTE and bleeding events.These will be specifically and directly solicited from participants at the study visits as a well as screened for in patients who do not directly report events. Patients will be referred to their treating provider for management. See section 7.4 for further detail on the screening for and management of VTE and bleeding events.

Additional adverse events will be screened for during telephone calls at POD 30 and POD 90. The AE assessment period will start when participants are discharged as this coincides with

the start of the study intervention. Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of the investigator, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity

SAEs discovered in telephone calls will be immediately referred to a study investigator, who will review the event, possibly contact the participant to ensure they are referred to an appropriate level of immediate management, and notify the participant's treating clinician for any further management. The SAE form will be completed, including start and stop date, description, and grade according to the CTCAE version 5 (full guideline: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf):

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

AEs will also be categorized by their possible relatedness to the VTE prophylaxis as follows:

1. Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to prophylactic anticoagulant administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the prophylactic anticoagulant should be clinically plausible.
2. Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the prophylactic anticoagulant is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge).
3. Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the prophylactic anticoagulant).

However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).

4. Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to prophylactic anticoagulant administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the prophylactic anticoagulant) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
5. Unrelated – The AE is completely independent of prophylactic anticoagulant administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

AEs will be categorized as at least "Possibly Related" (or "Probably" or "Definitely") if the AE is listed as a possible event on the applicable drug label. Any SAEs or events that are bothrelated to participation in the trial ("Possibly" or higher) and also unexpected in terms of their nature or severity such that it suggests that the research places subjects or others at a greater risk of harm than was previously known will be reported to the IRB for further review.

10.5 Medical Monitor

The study will assign a Medical Monitor (MM) for approval by the Clinical Trials Scientific Review and Monitoring Committee. The Medical Monitor will be tasked with monitoring the adverse events captured in this study (see previous section 10.4). They will have access to all study data for their review including access to adverse event forms, PHI and patient medical charts, drug labels, study questionnaires, and study protocol.

The Medical Monitor will be either an internal or external expert however they will not be a collaborator with the PI. They will not be compensated. The MM may resign from this role at his/her discretion. A thirty-day notification should be provided to the PI to allow for a replacement MM to be appointed.

The MM will have the authority to request a study hold or discontinuation. The MM may also at his/her discretion report information to and/or consult with other institutional oversight committees such as the University of Pennsylvania IRB when there are significant concerns about research safety and/or integrity. The MM is responsible for contacting the appropriate committee with any concerns related to his/her role as MM.

10.6 Unanticipated Problems

Beyond medical complications, any event or incident during the trial that is unexpected in nature and severity, possibly related to the trial, and suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously recognized will be considered an "Unanticipated Problem" and will be reported to the IRB as soon as it is recognized. Complete cooperation with the IRB and any other regulatory bodies thereafter will be supplied.

10.7 Compensation

Participants at the University of Pennsylvania will be given a $20 Greenphire ClinCard, either electronic or physically mailed based on patient preference, at the completion of the study as a gesture of thanks for their time in participating. Receipt is contingent only on completing both study visits. This effort is supported by the American Urologic Association Resident Research Award.

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