PREVENTION OF VENOUS THROMBOEMBOLISM FOLLOWING RADICAL PROSTATECTOMY

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Title: A Randomized Controlled Trial for Prevention of Venous Thromboembolism following Radical Prostatectomy

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

This research proposal aims to evaluate the PREvention of VENous ThromboEmbolism (VTE) following Radical prostatectomy (RP) for prostate cancer (the PREVENTER trial) by comparing the use of perioperative pharmacologic prophylaxis (subcutaneous heparin) with intermittent pneumatic compression devices (IPCs) to the use of IPCs alone. Currently, there is no standard practice for VTE prophylaxis after RP with the American Urological Association recommending "pharmacological or pneumatic mechanical prophylaxis" for high risk patients. Prior studies showed 30% of patients in the United States received no perioperative prophylaxis and less than 20% received pharmacologic agents, compared to 98% of patients receiving pharmacologic prophylaxis in the United Kingdom. Some urologists prescribe patients low molecular weight heparin (LMWH) after discharge for up to 30 days after surgery. Additionally, there are no established risks of pharmacologic prophylaxis for RP patients, but some urologists express concern about the potential impact of prophylaxis on the rate of postoperative lymphoceles or hematomas. At Johns Hopkins, patients do not routinely receive pharmacologic VTE prophylaxis in the perioperative setting for RP. Given the lack of standard practice and implications for patient safety, we propose a randomized controlled trial to evaluate the impact of perioperative pharmacologic prophylaxis on VTE following RP hypothesizing that it will prevent VTE events without significantly impacting the rate of postoperative bleeding or lymphoceles.

2. Objectives (include all primary and secondary objectives)

Specific aims: Does the use of perioperative pharmacologic agents (subcutaneous heparin; 5,000 units given before surgery and every 8 hours after surgery until discharge), compared to IPCs alone, for RP for prostate cancer:

1. Prevent the occurrence of symptomatic VTE following surgery? (primary efficacy outcome)
2. Increase the incidence of clinically significant lymphocele? (primary safety outcome)
3. Increase the incidence of clinically significant hematoma? (primary safety outcome)
4. Increase the incidence of major bleeding following surgery? (primary safety outcome)
5. Prevent the occurrence of any VTE (asymptomatic or symptomatic) following surgery? (secondary outcome)
6. Increase estimated blood loss during surgery? (secondary outcome)
7. Increase surgical drain output after surgery? (secondary outcome)

8. Lead to potential surveillance bias measured by increased or decreased use of diagnostic imaging for VTE relative to symptoms (e.g. lower extremity Duplex ultrasound, spiral CT angiography, V/Q scan, etc.)? (secondary outcome)

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

An estimated 180,000 new cases of prostate cancer were diagnosed in 2016, and about 90,000 radical prostatectomies are performed in the United States annually [1-3]. Since the year 2000, a sharp change in practice patterns has shifted the traditionally open radical prostatectomy (RP) procedure to current practice where the great majority (likely >70%) are robotic-assisted laparoscopic RPs (RALRP) [3]. According to most guidelines, undergoing RP by any approach classifies a patient as high-risk for venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), and would lead to implementation of appropriate intermittent mechanical pneumatic compression devices (IPCs) and pharmacologic prophylaxis [4-8].

Early reports of VTEs after prostatectomy noted variable rates from 20% to 50% using screening studies that implemented 125 I-fibrinogen scanning, which has since been outdated due to questionable specificity [9-11]. During the era of Walsh's anatomical approach to the RRP, one series reported a clinical post-operative PE incidence of 2.7% [12-14]. More recent studies attempting to estimate postoperative VTE rates have been flawed by lack of consistent or planned follow-up to specifically monitor symptoms of VTE. Modern rates are thought to have significantly decreased, about 3 to 8-fold in the past 20 years, due to shorter hospital stays, early ambulation, and the advent of robotic and laparoscopic techniques [15]. Current estimates of symptomatic VTE range from 0.2% to 8% with a recent series implementing both mechanical and pharmacologic prophylaxis reporting a rate of 1-2% with several-fold greater risk for undergoing concurrent lymphadenectomy or open surgical approach [15,16]. Generally, the best available evidence is largely derived from series where all patients receive pharmacologic prophylaxis with an overall rate of about 2% [16-19].

One retrospective study of laparoscopic RP at high-volume centers with no planned follow-up for VTE reported 27 imaging confirmed DVTs and 9 imaging confirmed PEs in 31/5951 (0.5%) patients where over two-thirds received some degree of heparin prophylaxis [20]. The thoroughness of follow-up and events captured across centers, unfortunately, appeared unreliable. For example, one surgeon who utilized preoperative and postoperative heparin prophylaxis reported an overall VTE rate of 6.2% (4.9% DVT, 1.2% PE) while all other surgeons reported rates of <1%. An administrative series from the National Surgical Quality Improvement Program captured a PE rate of 32/8381 (0.4%) after laparoscopic RP, which suggests many more patients would have had symptomatic DVTs making the overall VTE rate several-fold greater [21]. Very few screening studies have been performed in this setting. One study from Indiana performed screening ultrasonography within 1 week of surgery to identify a DVT in 2/245 patients, but an additional 7 patients (3.7% overall) with initially negative ultrasonography presented symptomatically within 2 weeks after surgery, 2 of whom developed PEs [22]. A Chinese screening study detected DVTs in 18/109 (16.9%) patients on postoperative day 3 after RALRP, although only 1 patient had an above the knee DVT requiring anticoagulation [23].

However, controversy remains as to whether pharmacologic prophylaxis significantly contributes to reduced rates of VTE for patients undergoing RP in the modern era of RRP and RALRP. In addition, some urologists have been wary due to an early report, based on 38 patients, of increased rate of lymphoceles associated with subcutaneous heparin after RRP with pelvic lymphadenectomy [24]. Notably, a report from almost 20 years later analyzing 579 patients receiving pelvic lymphadenectomy (533 had concurrent RRP) showed no statistically significant difference in lymphocele rate by screening pelvic ultrasound [25]. No randomized controlled trial has been performed to assess reduction in rates of VTE due to pharmacologic prophylaxis or potential increase in complications such as bleeding and lymphocele.

Because of this, the American Urological Association Best Practice Statement leaves open the possibility for substantial variations in practice in the United States [26]. An estimated 17.8% of patients in the United States received any pharmacologic VTE prophylaxis following RP and 30.0% received no prophylaxis at all [27]. Some urologists prescribe patients LMWH after discharge for up to 30 days after surgery. In stark contrast, 98% of patients receive pharmacologic prophylaxis after RP in the United Kingdom, in line with guidelines from their National Clinical Guideline Centre, and 61% receive some form of post-discharge prophylaxis [6,7,28]. As others have recognized, the wide practice variation echoes a dire need to quantify the potential benefits and harms of pharmacologic VTE prophylaxis after RP [4].

At Johns Hopkins, current practice for RP patients employs IPCs during hospitalization but no routine use of pharmacologic prophylaxis. However, perioperative pharmacologic prophylaxis is employed for the majority of other major urologic cancer surgery, including kidney and bladder cancer. For example, in the case of radical cystectomy (bladder removal for bladder cancer), preoperative subcutaneous heparin (5,000 units) is administered to all patients and all patients receive 5,000 units every 8 hours while they are in the hospital. Patients are routinely switched to low molecular weight heparin (LMWH) prophylaxis before discharge and prophylaxis is continued after discharge for up to 30 days from surgery. In the case of nephrectomy, patients routinely receive subcutaneous heparin (5,000 units) postoperatively every 8 hours until discharge. For most patients undergoing a major operation with our general surgeons at Johns Hopkins, especially for a cancer diagnosis, subcutaneous heparin (5,000 units) or LMWH is administered preoperatively and every 8 hours postoperatively. Our practice with RP, as well as that of other urologists in the United States, is a unique exception to the general trend that suffers from lack of level 1 evidence. VTE prophylaxis is a core performance measure endorsed by The Joint Commission and the National Quality Forum. Therefore, a randomized trial could help inform the need for and safety of pharmacologic VTE prophylaxis in the RP population to establish a more uniform standard of practice and develop a more appropriate health quality and patient safety benchmark specific to RP.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

The study will be a randomized controlled trial of RP patients randomized to receive perioperative pharmacologic prophylaxis (subcutaneous heparin; 5,000 units given before surgery and every 8 hours after surgery until discharge) with IPCs or routine care with IPCs alone. No other standard post-RP practices will be affected. Per routine, all patients will be encouraged to ambulate early.

Routine care includes an initial clinic consultation, a preoperative evaluation center (PEC) visit prior to surgery (often done the day before surgery), and a planned 1 to 2 night inpatient stay after surgery. Patients currently receive IPCs but no pharmacologic prophylaxis in our default practice at Johns Hopkins. Patient are often given the option of returning to the Johns Hopkins clinic or local follow-up (with a provider or at home) for urinary catheter removal at around 10 days from surgery. Patients who were referred by outside urologists or providers may then decide if they wish to be followed at Johns Hopkins or locally for routine post-RP surveillance for cancer recurrence. Our current default practice at Johns Hopkins of no pharmacologic prophylaxis is considered inappropriate for most other major surgeries. However, both arms of this trial are considered routine standards of practice in the United States.

Informed consent will be obtained before surgery at either their urology or PEC clinical visit, or in the preoperative area the day of surgery. Eligibility will be confirmed at the time of consent. Patients will be randomized after consent is obtained and their surgery is officially scheduled to minimize dropout. Randomization will be done in blocks and stratified by whether patients choose to undergo an option 30-

day lower extremity Duplex ultrasound (outlined below) and whether they are having open or minimally-invasive (robotic/laparoscopic) surgery.

Patients randomized to the pharmacologic VTE prophylaxis arm will receive a dose of subcutaneous heparin 5,000 units within 2 hours prior to incision, and subcutaneous heparin 5,000 units every 8 hours after surgery until discharge. Total number of doses received and missed doses will be recorded. No post-discharge pharmacologic prophylaxis will be prescribed. Per routine care, patients will be requested to inform their urologist's office if they experience any symptoms of DVT or PE, or any other concerns, during the first 30 days after surgery. All patients will receive a phone call around 30 days after surgery to assess primary outcomes including documentation of whether they experienced a postoperative VTE episode and any treatment initiated for confirmed VTE. Any patient endorsing symptoms concerning for VTE up to 30 days after surgery will be recommended to undergo urgent evaluation and care, locally or at Johns Hopkins, with imaging/evaluation results forwarded to Johns Hopkins. Patients and their insurance will be responsible for the costs as part of routine care. The 30-day phone call will be the only planned, study-initiated contact after surgery with the patient to evaluate symptomatic outcomes and will be the same for both the control and pharmacologic prophylaxis arms.

An optional part of the study protocol, a subcohort of at least 200 patients (funds allowing) will be offered a routine 30-day post-RP screening lower extremity Duplex ultrasound to assess for DVT at Johns Hopkins for patients willing to travel to Johns Hopkins to obtain the ultrasound in this time frame. Patients are not required to obtain this screening ultrasound, but initial randomization will be stratified by whether patients opt to undergo ultrasound (and robotic vs. open surgery) to ensure study arms are balanced. In other words, patients willing to undergo ultrasound will be identified before randomization. All patients, regardless of whether they undergo ultrasound, will be assessed for all primary outcomes as described. For the subset of patients who obtain the ultrasound, it will be used to assess the secondary outcome of any VTE (asymptomatic or symptomatic). The outcome of any VTE will be tabulated based on the results of the screening ultrasound and any report of a symptomatic VTE episode (assessed by call at 30 days as described above). Stratified randomization is outlined in Figure 1. Written informed consent includes a plan to inform the patient and their primary physician of the results of the ultrasound and any incidental findings. Costs for the screening ultrasound obtained as part of the study will be covered by the study. Symptoms prompting a recommendation for evaluation to rule out DVT or PE (appropriate diagnostics/imaging to be determined by evaluating physician) will include:

1. Persistent unilateral or bilateral lower extremity edema
2. Persistent calf pain or cramping
3. Persistent or new chest pain
4. Persistent or new shortness of breath that started suddenly or worsens with exertion
5. Productive cough with bloody sputum
6. Fever and/or tachycardia without any known source of infection
7. Any other clinical concern for DVT or PE

The primary efficacy outcome will be the incidence of symptomatic VTE. The primary safety outcomes will include three separate measures of incidence of symptomatic lymphocele, incidence of symptomatic hematoma, or major bleeding within 30 days after surgery. The secondary outcomes (all regarded separately) will be estimated blood loss from surgery, total surgical drain output after surgery (for patients with surgical drains), the overall incidence of VTE (asymptomatic or symptomatic) determined from the subcohort undergoing lower extremity Duplex screening ultrasound, and surveillance bias (measured by use of postoperative diagnostic imaging, either as inpatient or within 30 days from surgery). Two planned interim analyses will be conducted as outlined in the study statistics section with early stopping rules due to adverse events or demonstrated futility.

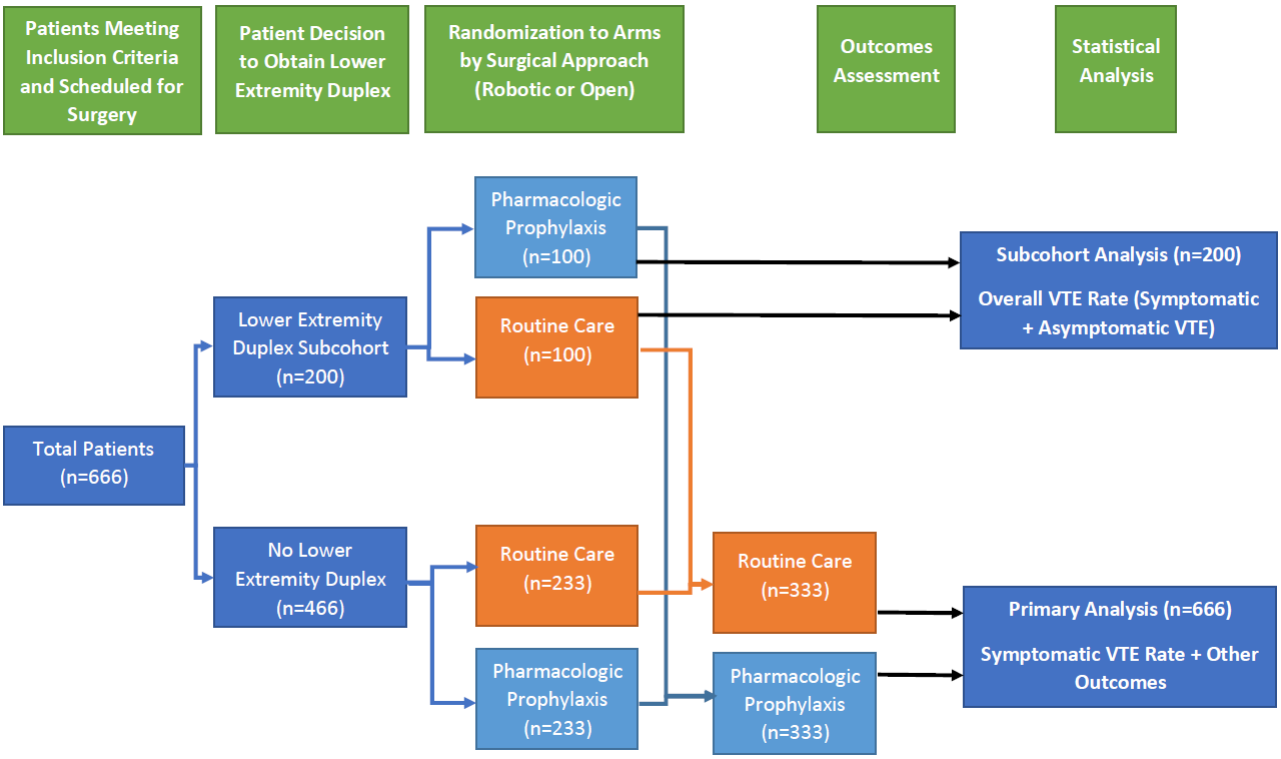

Figure 1. Diagram of plan for stratified randomization of patients to arms and outcomes assessed.

b. Study duration and number of study visits required of research participants.

The study protocol will be largely implemented during routine visits required of all RP patients (described above) with the addition of a visit specifically for screening lower extremity Duplex for eligible patients as part of the run-in described above. Patients will be contacted by phone around 30 days after surgery to tabulate the primary and secondary outcomes. Patients may initiate contact before this point if they wish to report concerns or diagnosis of VTE. Any events that occur after 30 days and are reported by patients in an unsolicited fashion will be documented, but they will not be included as part of the primary outcome. There will be no planned contact initiated by the study team with patients after 30 days except to confirm documentation of VTE events that occurred up to 30 days from surgery due to symptoms or discovered on screening lower extremity Duplex ultrasound. Patients reporting symptoms concerning for VTE at or before the 30 day mark who are diagnosed within 2 weeks of reporting symptoms (even if after the 30 day mark) will be included as symptomatic VTE events for the primary outcome.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Urologists will initially be blinded to patient randomization and the administration of the preoperative subcutaneous heparin dose to prevent bias on recorded estimated blood loss during the surgery. Postoperatively, administration of subcutaneous heparin will be unblinded during the patient's inpatient stay. Control patients will receive IPCs only and no placebo doses will be administered during their hospital stay. Data analysis will be blinded as to treatment group. Performance and interpretation of lower extremity Duplex screening ultrasound will be blinded to patient randomization. Surveillance bias will be assessed by differential performance of postoperative imaging as described above.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All patients will receive routine care. Both arms include patients receiving accepted standards of care.

e. Justification for inclusion of a placebo or non-treatment group.

The control group in this trial is the group receiving current routine practice at Johns Hopkins with IPCs. The experimental group is the group receiving pharmacologic VTE prophylaxis as practiced at other centers and recommended by most VTE guidelines for major surgery.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the trial if surgery is canceled or not completed for any reason. All patients assigned to the experimental and control arms completing surgery will be included in the study regardless of compliance with pharmacologic prophylaxis doses in an intention-to-treat (ITT) analysis. Patients experiencing an adverse event will be provided appropriate care. Additional per-protocol analyses will be conducted to compare outcomes by compliance with assigned regimen. Patients diagnosed with VTE events will be recommended to obtain routine care locally or at Johns Hopkins per patient preference.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Perioperative pharmacologic prophylaxis is only given during the patient's inpatient stay. As mentioned above, all patients will be included in an ITT analysis as possible if they undergo surgery. No planned outcomes will be tracked after the 30-day post-surgical outcomes unless the patient initiates contact.

5. Inclusion/Exclusion Criteria

Inclusion:

1. Men 18-100 years of age with histologically confirmed prostate cancer of any stage undergoing RP
2. Normal preoperative coagulation blood test (prothrombin time)
3. Patients who would have otherwise been eligible to receive routine post-RP care

Exclusion:

1. Active treatment for VTE
2. Patients judged by their urologist or PEC center to be unsafe to forgo pharmacologic prophylaxis or systemic anticoagulation postoperatively (whether or not they are on systematic anticoagulation for indications other than VTE)
3. Known adverse reactions to heparin (heparin-induced thrombocytopenia or any allergy)
4. Epidural analgesia
5. Spinal anesthesia
6. Participation in a different trial that increases a patient's risk of VTE

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Subcutaneous heparin and LMWH are routine agents for perioperative pharmacologic VTE prophylaxis. No randomized controlled trials have evaluated their use in the RP population to prevent VTE in the modern area of early ambulation and IPCs. A retrospective study reported that while LMWH reduced the rate of VTE, it could potentially increase the overall rate of bleeding/hematomas and lymphoceles compared to not receiving LMWH [29]. Subcutaneous heparin, however, does not appear to increase the rate of postoperative pelvic lymphoceles evaluated by screening ultrasound [25]. Additionally, subcutaneous heparin and LMWH were found to be equally effective at preventing VTE in a colorectal population [30]. Therefore, to minimize risk of complications and derive the greatest potential benefit, patients will receive standard prophylactic dosing of subcutaneous heparin at 5,000 units once before surgery (within 3 hours prior to incision) and then every 8 hours postoperatively.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A – drugs are being used for approved indications.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A – drugs are being used for approved indications.

7. Study Statistics

a. Randomization scheme.

Randomization by blocks will be used, with stratification for type of surgery (robotic/laparoscopic vs. open) and subcohort membership (agrees to 30 day ultrasound/does not agree to 30 day ultrasound). Currently at Johns Hopkins approximately 40% of RPs are performed open, with the remainder robotic or laparoscopic, and the subcohort is planned to include 200 patients. Note that patients are randomized within each of the 4 subgroups formed by cross classification of these 2 strata, not randomized to the strata. Therefore, anticipated sizes of the 4 strata are

1. open RP/subcohort member, n=80
2. open RP/not subcohort member, n=186
3. robotic RP/subcohort member, n=120
4. robotic RP/not subcohort member, n=280

Because the above numbers are subject to variability in the choice of surgical approach, randomization lists will increase the number in each of the surgical categories by 20%, i.e. 320 and 480 random assignments will be generated for open and robotic surgeries, respectively. An undisclosed block size will be used to prevent any ability to predict next treatment assignment. The randomization lists will be generated by Dr. Trock using SAS PROC PLAN. Although this uses a pseudorandom number generator it has the advantage of reproducibility when the same seed is used. Dr. Trock will maintain the randomization list, password protected, on a remote drive maintained by the Department of Urology, and will provide the random assignment to the study coordinator as each patient is enrolled. Because surgery dates are scheduled weeks in advance, there is no concern about inability to access the randomization list. A biostatistician who works for Dr. Trock and is not otherwise connected to this trial will also have access to the random assignments and can provide them to the study coordinator in the unlikely event that Dr. Trock is unavailable. Only Dr. Trock and the biostatistician (Zhaoyong Feng) have access to the remote drive.

b. Primary outcome variable.

The primary efficacy outcome will be the incidence of symptomatic VTE within 30 days after surgery. A symptomatic VTE event will be defined as any imaging-confirmed VTE diagnosed after evaluation for VTE prompted by the presence of signs/symptoms concerning for VTE. The primary analysis will compare this rate between treatment arms at the 30-day follow-up for all patients. Symptomatic VTE will also include any deaths attributed to a clinically suspected VTE event without imaging confirmation (if autopsy is performed, VTE must be confirmed at autopsy; if autopsy is not performed, clinical suspicion of VTE as the cause will suffice). Symptoms prompting evaluation include:

1. Persistent unilateral or bilateral lower extremity edema
2. Persistent calf pain or cramping
3. Persistent or new chest pain
4. Persistent or new shortness of breath that started suddenly or worsens with exertion
5. Productive cough with bloody sputum
6. Fever and/or tachycardia without any known source of infection
7. Any other clinical concern for DVT or PE

The primary safety outcomes will include three separate measures of incidence of symptomatic lymphocele, incidence of symptomatic hematoma, or major bleeding within 30 days after surgery. Symptomatic lymphocele and symptomatic hematoma will include imaging confirmed events based on imaging pursued at the discretion of the primary attending urologist per routine practice (current routine practice involves imaging only if clinical symptoms suggest possibility of a lymphocele or hematoma). Events will be recorded regardless of the need for intervention (e.g. drain placement by interventional radiology). While screening studies show rates of 25-50% for postoperative lymphocele regardless of surgical approach (open or robotic), the rate of symptomatic lymphocele is thought to be around 10% or less [31,32]. Major bleeding will be defined as the need for transfusion of ≥2 units of packed red blood cells after the completion of surgery for anemia attributed to postoperative bleeding or need to return to the operating room for active bleeding.

c. Secondary outcome variables.

The secondary outcomes (all regarded separately) will be estimated blood loss from surgery, total surgical drain output after surgery (for patients with surgical drains), the overall incidence of VTE (asymptomatic or symptomatic) determined from the subcohort undergoing lower extremity Duplex screening ultrasound, and surveillance bias (measured by use of postoperative diagnostic imaging). Estimated blood loss will be recorded from the anesthesia data report from surgery. Total surgical drain output will be recorded based on ins and outs flowsheets routinely recorded by nurses when emptying drains. Surveillance bias will be determined by recording the type and frequency of postoperative imaging performed while a patient is in the hospital or within 30 days of surgery after discharge.

The overall rate of VTE will only be determined for patients in the subcohort. The asymptomatic VTE will be determined based on the results of the screening lower extremity Duplex ultrasound for asymptomatic DVTs. The overall rate of VTE will be determined by adding the number of asymptomatic VTE events to the number of symptomatic VTE events experienced in the subcohort.

d. Statistical plan including sample size justification and interim data analyses.

Pharmacologic VTE prophylaxis can be expected to prevent between 67% to 75% of DVTs [33]. Given the lowest expected primary outcome event rate will be for VTE, the trial sample size will be based on a power of 80% (beta=0.2) and one-sided alpha of 0.05 for prevention of post-operative VTE with pharmacologic prophylaxis reducing the rate from 5% to 1.5%. Including two interim analyses of the primary endpoint as outlined in the Intermin Analyses section below, the total sample size needed will be 666 (333 per treatment arm) based on 2000 simulations for 82% power (exact alpha-spending and futility boundaries are outlined below). As mentioned above, the primary efficacy analysis will compare symptomatic VTE rates at the 30-day follow-up for all patients. Secondary analyses will be conducted to compare secondary outcomes between treatment arms at the completion of the study as well. It is expected that during full-time patient enrollment, the study would require about 2 years to accrue patients assuming 50% enrollment.

Two planned interim analyses of the primary endpoint will be conducted, after one-third and two-thirds of patients have undergone RP. Early stopping for efficacy or futility will be assessed at these time points. Details are provided below under Interim Analyses.

Statistical analyses: The treatment and control groups will be compared to identify any imbalance after randomization in relevant characteristics. Comparisons will include factors such as age, race, BMI, comorbidities, prostate volume, tumor stage, operative time, and blood loss. Discrete factors will be compared with chi-squared test, and continuous factors will be compared with t-test or Wilcoxon ranksum test if data do not conform to a Gaussian distribution. Analysis of the primary outcome (symptomatic VTE) will compare 30 day post-RP rates between the treatment and control groups, using chi-squared test. Logistic regression will be used if adjustment is required for any potential confounders not balanced by randomization, with the treatment effect estimated by the odds ratio and 95% confidence interval. Similar comparison of univariate rates, and adjusted odds ratios will be used for the 3 primary safety endpoints (lymphocele, hematoma, occurrence of major bleeding), and for the secondary outcome of any VTE (restricted to patients who undergo the 30 day lower extremity Duplex ultrasound). Secondary endpoints with a continuous metric (blood loss, surgical drain output, number of imaging tests (surveillance bias)) will be compared in univariate fashion using t-test or Wilcoxon ranksum, and adjusted analyses will use linear regression. Note that analysis of drain output is confined to patients with drains placed, so it is not protected by the randomization, potentially limiting interpretability if the number of patients is small and confounding factors are not well balanced. All analyses of primary and secondary outcomes will be based on intention to treat (ITT). Per protocol analyses will also be conducted, but treatment success will be based on ITT.

Additional subanalyses (both ITT and per protocol) will be performed with stratification by arm compliance (proportion of scheduled subcutaneous heparin doses administered), performance of pelvic lymphadenectomy (including number of nodes removed), performance of open or robotic surgery (including differences in operative time), and other demographic and comorbidity criteria (including history of VTE, cancer, and other risk factors included in the Caprini Score) to identify patients at highest risk for VTE. Surveillance bias will also be evaluated, as mentioned above, by the differential performance of diagnostic imaging.

e. Interim Analyses.

Two interim analyses of the primary endpoint are planned with potential early stopping for efficacy or futility. O'Brien-Fleming boundaries were used, as implemented in PASS v. 11 (NCSS Software, Inc., Kaysville, UT). The total sample size needed for 82% power with a 1-sided test is 666 (333 per treatment arm), based on 2000 simulations. The interim analyses will be conducted after 1/3 and 2/3 of patients are enrolled (222 and 444, respectively). Alpha-spending at the 2 interim analyses and final analysis is .001,

.015, and .033 (cumulative alpha spent .001, .015, .048), respectively. The futility boundaries at the 1st and 2nd interim analyses, and final analysis are p=0.816, 0.272, and 0.070, respectively.

At each interim analysis the rates of the 3 safety endpoints (lymphocele, major bleeding, and hematoma) will also be evaluated and 95% confidence intervals calculated. Unacceptable rates for these endpoints are $\geq$15%, $\geq$5%, and $\geq$10%, respectively. If lower 95% confidence bounds meet or exceed these unacceptable rates the trial will be halted for further review and consideration of early stopping.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Administration of subcutaneous heparin:

1. Major risks:
    a. Heparin-inducted thrombocytopenia (HIT; very rare): While up to 5% of patients receiving IV unfractionated heparin may develop HIT, a large series noted a rate closer to 1% for therapeutic-dosed IV heparin and a very rare incidence (<0.1%) of suspected cases for prophylactic subcutaneous heparin (same regimen patients in this trial will receive) [34]. Notably, HIT usually occurs at 5-10 days of starting therapy, and the vast majority of patients in this trial will be discharged by postoperative day 2, greatly reducing exposure.
2. Minor risks:
    a. Bruising at injection site (short-lived but can be common)
    b. Pain/discomfort (minor but can be common during injection)

b. Steps taken to minimize the risks.

Subcutaneous heparin for VTE prophylaxis is given commonly on most medical and surgical floors at Johns Hopkins. Careful medication administration will help minimize risk of bruising and pain. HIT is observed very rarely, as mentioned above, and any patients who will have extended exposure (>3 days) will have their platelet counts monitored by routine complete blood counts.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or concerns will be reported by the in-hospital urology team to the research coordinator(s) of the trial as well as the principal investigator. A plan of action will be developed and implemented with open communication with the IRB and appropriate avenues for reporting adverse events. The Hopkins Event Reporting Online (HERO) system can also be utilized as needed. Compliance with administering subcutaneous heparin doses will be monitored and handled accordingly as mentioned in the study statistics section).

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are no anticipated legal risks with breach of confidentiality specifically associated with the trial. After surgery, administration of subcutaneous heparin will be unblinded. Patients participating in the trial will receive the usual care afforded to all RP patients.

e. Financial risks to the participants.

Both arms of the trial consistent of accepted practice standards. Patients and their respective insurance will be responsible for the cost of routine care including surgery, inpatient care including

room/board/medications, and postoperative follow-up (including diagnostics performed for symptoms) which will be unaffected by the study. Screening lower extremity Duplex ultrasound at 30 days will be optional with the associated costs covered by the study for patients who enroll. Standard medical treatment for diagnosed VTE events may be initiated at Johns Hopkins or locally at the hospital or medical center of the patient's choice with financial responsibility assigned to the patient and their respective insurance.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Patients participating in the trial in the control arm of routine IPC use will experience no benefits beyond receiving the routine perioperative care for RP patients at Johns Hopkins, which constitutes an acceptable standard of care. Patients in the experimental arm receiving pharmacologic VTE prophylaxis, which also constitutes an acceptable standard of care, may experience a reduced rate of VTE and subsequent complications such as death that may arise from VTE. The potential benefit for society would be the ability to reduce the rate of VTE and subsequent complications, including death, for patients undergoing RP (~90,000 annually in the United States) if pharmacologic prophylaxis is found to be beneficial. Another benefit for society would be the ability to establish a quality metric and reference values more specific to RP patients given the current level of practice variation.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will receive no compensation or penalties associated with completing or not completing the protocol.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The administration of subcutaneous heparin in the perioperative setting is an established method of VTE prophylaxis and will be included in the routine costs of surgical and inpatient care. The cost to participants will be negligible, estimated at ~$5 for 3 doses, for a total of $6.50 to $11.30 for the expected 4 to 7 expected doses during hospitalization [35]. These costs are generally covered by medical insurance.

For patients with symptoms or clinical concern for DVT or PE, evaluation will be recommended and costs of routine diagnosis and treatment will be assigned to the patients and their medical insurance. For asymptomatic patients who opt and enroll to have a 30 day post-RP screening lower extremity Duplex ultrasound (regardless of a prior negative or positive imaging/evaluation), costs will be covered by the study.

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